

## **LITERATURE-RELATED DISCOVERY (LRD)**

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## **ABSTRACT**

Discovery in science is the generation of novel, interesting, plausible, and intelligible knowledge about the objects of study. Literature-related discovery (LRD) is the linking of two or more literature concepts that have heretofore not been linked (i.e., disjoint), in order to produce novel, interesting, plausible, and intelligible knowledge (i.e., potential discovery). LRD has two main components that differ in their methodological approach to discovery:

- Literature-based discovery (LBD) produces potential discovery through analysis of the technical literature alone.
- Literature-assisted discovery (LAD) produces potential discovery through both analysis of the technical literature and use of selected authors of that literature. These authors generate potential discovery as proposers, workshop/panel participants, or in other active roles.

In turn, there are two types of LBD and LAD: open discovery systems (ODS), where one starts with a problem and arrives at a solution, and closed discovery systems (CDS), where one starts with a problem and a solution, then determines the mechanism(s) that links them.

LRD offers the promise of large amounts of potential discovery, for the following reasons:

- the burgeoning technical literature contains a very large pool of technical concepts in myriad technical areas;
- researchers spend full time trying to cover the literature in their own research fields and are relatively unfamiliar with research in other especially disparate fields of research;
- the large number of technical concepts (and disparate technical concepts) means that many combinations of especially disparate technical concepts exist

- by the laws of probability, some of these combinations will produce novel, interesting, plausible, and intelligible knowledge about the objects of study

This monograph presents the LRD methodology and voluminous discovery results from five problem areas: four medical (treatments for Parkinson's Disease (PD), Multiple Sclerosis (MS), Raynaud's Phenomenon (RP), and Cataracts) and one non-medical (Water Purification (WP)). In particular, the ODS aspect of LRD is addressed, rather than the CDS aspect. In the presentation of potential discovery, a 'vetting' process is used that insures both requirements for ODS LBD are met: concepts are linked that have not been linked previously, and novel, interesting, plausible, and intelligible knowledge is produced.

The potential discoveries for the PD, MS, Cataracts, and WP problems are the first we have seen reported by this ODS LBD approach, and the numbers of potential discoveries for the ODS LBD benchmark RP problem are almost two orders of magnitude greater than those reported in the open literature by any other ODS LBD researcher who has addressed this benchmark RP problem. The WP problem is the first non-medical technical topic to have been addressed successfully by ODS LBD.

In all cases, but especially the medical, we have barely scratched the surface of quantity and quality of potential discovery that could be generated with adequately resourced studies. Based on the many potential discoveries we have obtained, and the promise of far more potential discoveries with adequately resourced studies, we have generated a new paradigm relative to discovery: **while the key challenge in traditional discovery is finding a needle-in-a-haystack, the key challenge in ODS LRD (used appropriately) is handling the overwhelming amount of potential discovery available.**

Additionally, it is our thesis, as the specific ODS LBD studies will demonstrate, that **synergistic combinations of our mainly individual potential discoveries are themselves potential discoveries.** We demonstrate throughout this monograph the synergistic effects of combining a very few potential discoveries or interesting core literature concepts, and believe that these synergistic benefits are operable at larger scales of combination. In the final lessons-learned chapter of this monograph, we also show that providing evidence for the synergistic benefits of large numbers of potential

discoveries or interesting core concepts is very difficult due to the large numbers of potential combinations involved.

One variant of the LAD operational mode (identifying disparate discipline recipients for Broad Agency Announcement (BAA) notifications in order to stimulate proposals of new ideas from these disparate disciplines) is presented for WP. Other possible applications of LAD include:

1. Recipients of solicitation announcements (other solicitations similar to BAA, journal Special Issue calls for papers, etc),
2. Participants in Workshops, Advisory Panels, Review Panels, Roadmaps, and War Games,
3. Points of Contact for Field Science Advisors, Foreign Field Offices, Program Officer site visits, and potential transitions

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# Chapter 1 - LITERATURE-RELATED DISCOVERY: INTRODUCTION AND BACKGROUND

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## 1.0 INTRODUCTION

### 1.1 Purpose of Monograph

This monograph presents a comprehensive approach for systematic acceleration of discovery and innovation, and demonstrates the generation of large amounts of potential discovery through five case studies.

### 1.2 Why are discovery and innovation important?

Discovery and innovation are the cornerstones of frontier research. They are the foundation of modern competitive militaries and commercial economies. They allow the technologically advanced nations to remain competitive with the developing nations, which have large well-trained low-cost labor pools.

### 1.3 What do we mean by discovery and innovation?

Discovery is ascertaining something previously unknown or unrecognized. More formally, “Discovery in science is the generation of novel, interesting, plausible, and intelligible knowledge about the objects of study” [1]. It can result from uncovering previously unknown information, or synthesis of publicly available knowledge whose independent segments have never been combined, and/or invention. In turn, the discovery could derive from logical exploitation of a knowledge base, and/or from spontaneous creativity (e.g., Edisonian discoveries from trial and error). [2]. Innovation reflects the metamorphosis from present practice to some new, hopefully “better” practice. It can be based on existing non-implemented knowledge. It can follow discovery directly, or resuscitate dormant discovery that has languished for decades.

We can further stratify discovery into literature-related and non-literature-related. In the literature-related context (which is the focal point of this monograph), **discovery is linking two or more literature concepts that have heretofore not been linked (i.e., disjoint), in order to produce novel,**



***interesting, plausible, and intelligible knowledge***. Thus, simply linking two or more disparate concepts is a necessary, but not sufficient, condition for literature-related discovery. In particular, concepts may be disjoint because the value of their integration has not been recognized previously, or they may be disjoint because there appears to be little value in linking them formally. Examples of the latter (which had been published as potential discovery) will be shown in the Background section of this chapter.

Also, in the literature-related context, innovation is the exploitation of a discovery linkage, mainly the identification of a linkage that was not being exploited at a sufficient pace. As will be shown in the Background section, many of the potential discoveries claimed in the peer-reviewed literature may be innovations, since the generic concept connections had been identified previously.

More generally, ***radical discovery*** depends on the source of the inspiration and/or the magnitude of the impact. The more disparate the source of ideas from the target problem discipline, the more radical the potential discovery. The greater the magnitude of change/impact resulting from the discovery, the more radical the potential discovery. The emphasis of the present monograph is on identifying myriad disparate sources using text mining principles (where text mining is the extraction of useful information from large volumes of text).

#### 1.4 Why is concept linkage among disparate literatures important and difficult?

One of the methods for generating discovery in a target discipline is use of principles and insights from disciplines very disparate to the target discipline, in order to solve problems in the target discipline. The challenge has become more critical due to increasing specialization and effective isolation of technical/medical researchers and developers [3]. As research funding and numbers of researchers have increased substantially over the past few decades, the technical literature has increased substantially as a result. Researchers/developers struggle to keep pace with their own disciplines, much less to develop awareness of other disciplines. Thus, we have the paradox that the *expansion of research* has led to the *balkanization of research*! The resulting fragmentation serves as a barrier to cross-discipline knowledge transfers, and retards the progress of discovery and innovation [3].

As a result, identifying these linkages between the disparate and target disciplines, and making the subsequent extrapolations, has tended to be a very serendipitous process. For the past two decades, there have been many attempts to link diverse disciplines systematically for the purpose of generating and accelerating discovery. These attempts can be subsumed under the heading of LRD.

### 1.5 What is Literature-Related Discovery Generally?

LRD is a systematic approach to bridging unconnected disciplines based on text mining procedures [4]. The front-end component identifies, retrieves, and characterizes the disparate literatures related to some target core literature, and the back-end component links concepts from the disparate literatures to the target core literature to generate potential discovery.

There are two main text mining avenues for extrapolating knowledge and insights from one discipline/ technology to another: **LBD** and **LAD**. The **LBD** approach uses technical experts to access and examine the literature from non-core disciplines to help solve problems in the core discipline. The **LAD** approach uses technical experts from non-core disciplines in a variety of interactive and/or independent creative modes for the same purpose. This monograph will focus mainly, but not exclusively, on ODS LBD. Both the ODS LBD and ODS LAD concepts have been described in detail [4].

### 1.6 What is Literature-Based Discovery Specifically?

ODS LBD is assumed to have originated with Swanson's 1986 paper in which he searched for potential RP treatments [5]. The general theory behind Swanson's LBD approach (both ODS and CDS), applied to two separate literatures, is based upon the following considerations.

Assume that two disjoint literatures can be generated, the first literature AB having a central theme "A" and sub-themes "B," and the second literature BC having central theme(s) "B" and sub-themes "C." Further, assume that linkages can be generated through the "B" themes that connect both literatures (e.g., AB-->BC). Those linkages that connect the disjoint components of the two literatures (i.e., the components of AB and BC whose intersection is zero) are candidates for discovery, since the disjoint themes

"C" identified in literature BC could not have been obtained from reading literature AB alone.

One interesting finding from Swanson's initial paper was that dietary eicosapentaenoic acid (theme "A" from literature AB) can decrease blood viscosity (theme "B" from both literatures AB and literatures BC) and alleviate symptoms of RP (theme "C" from literature BC). There was no mention of eicosapentaenoic acid in the RP literature, but the acid was linked to the disease through the blood viscosity themes in both literatures.

### 1.7 Why do we believe ODS LBD can generate potential discovery?

The technical/medical literature consists of many technical/medical concepts, each having its own sub-literature. Many, if not most, of these sub-literatures will be very disparate from each other. From a pure combinatorial perspective, there are large numbers of possible combinations of two, three, or more concepts. Many of these combinations will consist of fully disjoint literatures. Since we know from experience that many problems require multiple concepts for solution (multi-disciplinary, interdisciplinary), then we can hypothesize that the large number of potential combinations of concepts must include some fraction where the combination leads to potential discovery (generation of novel, interesting, plausible, and intelligible knowledge about the objects of study). We believe (and will demonstrate in this monograph) that a well-designed discovery search process will allow these potential discovery combinations to be identified and extracted with reasonable efficiency.

### 1.8 What are the metrics of ODS LBD progress?

A central problem with all the ODS LBD studies that have been reported in the open literature is the absence of a 'gold standard' that can be used as a basis of comparison [6]. A true 'gold standard' would allow comparisons of quality and quantity of potential discoveries. Many of the studies use Swanson's results (Fish Oil and Eicosapentanoic Acid for treatment of Raynaud's Phenomenon) as a comparison standard. As we point out in the Background section, we have questions as to whether Swanson's hypotheses are discoveries or innovations. In other words, was Swanson the first to link fish oil/eicosapentaenoic acid to the treatment of RP, or had the linkage been made previously, with Swanson's observations serving to accelerate the use

of fish oil/eicosapentaenoic acid to treat RP? In any case, his results give no indication of the extent of discoveries possible.

In science, if we want to estimate the quality of a predictive tool, we have two main choices. If we have an exact solution to the problem, we can compare the solution the predictive tool provides to the exact solution, and estimate the error as the difference between the exact solution and the predictive tool solution. Alternatively, if we have some way of estimating the error that accompanies a predictive tool solution, we can estimate the accuracy by that approach.

In LBD, and probably most methods of discovery, we don't know the extent of discovery possible for any problem, and are not able to estimate the comprehensiveness of any approach (recall). Further, we are not able to estimate the quality of any discovery until much testing has been done, which means that a long time will be required before we can state definitively the fraction of estimated potential discoveries that are real potential discoveries (precision).

#### 1.9 How rapidly has ODS LBD progressed since its inception?

ODS LBD intrinsically has powerful capabilities, and one would have expected that, since its inception in 1986, there would be treatments proposed for all the major chronic diseases, similar implementations for their non-medical equivalents, as well as major sponsored research programs on ODS LBD throughout the world. As far as we know, benefits resulting from these ODS LBD studies have yet to be realized.

#### 1.10 Why has progress in ODS LBD been so slow?

As will be obvious from the literature survey in the Background section, a major roadblock to wider-scale acceptance of ODS LBD has been its inability to generate real potential discovery, systematically, and on a wide scale. For the ODS LBD approaches reported in the literature, we have serious questions about whether any of them have generated discovery. In [7,8], we address some examples of reported 'discovery' about which we have some concern. For example, our definition of ODS LBD requires both a) no prior art and b) the addition of value. In these examples of 'discovery' that have been reported in the literature (addressed later in this chapter and

in more detail in [7,8]), we show that either a) prior art existed in the mainline literature, or b) the value added was questionable.

Given:

- the length of time since Swanson's pioneering paper (two decades),
- the massive number of medical and technical problems in need of radical discovery,
- the relatively few articles published in the literature using existing ODS LBD approaches to generate radical discovery (especially articles not published by the Swanson/ Smalheiser team and not replicating the initial Raynaud's results), and
- concerns about the validity of the discoveries reported

**it is clear that improvements in the strategic ODS LBD approach and its dissemination and acceptability are required.**

#### 1.11. What does this monograph contribute to ODS LBD

The main thesis of this monograph is that the scientific community has not made adequate use of these non-core discipline sources of knowledge to accelerate potential discovery. Further, very substantive quality enhancements to funding agency S&T programs, individual research projects, journal Special Issues, and multi-disciplinary teams and organizations are possible at relatively small marginal costs, if we can systematically improve access to the limitless sources of 'external' discipline/ technology information. Until now, there has been no fully systematic approach to bridging these unconnected target and disparate disciplines. This monograph describes a systematic approach for making these connections.

**Once the principles and associated techniques have been established for producing insights from disparate literatures, many applications are possible.** These include:

- 1) Promising opportunities for researchers to pursue
- 2) Promising new science and technology (S&T) directions for program managers to pursue
- 3) Promising leads for science and emerging technology analysts to pursue

## 1.12. What is the Structure of this Monograph?

The present chapter sets the stage for presentation of the studies, and lessons learned for future improvements. It starts by defining discovery and innovation, providing reasons for their importance and time criticality, and then describing the particular type of LRD (ODS LRD) that constitutes the main topic of this monograph.

The remainder of this monograph provides a summary of ODS LRD research, the general approach we have developed to overcome the limitations of past studies, and examples of problems for which we have generated large amounts of potential discovery through connecting concepts from disparate disciplines. The next section of this chapter presents a survey of the ODS LRD literature since its inception in 1986, emphasizing the limitations of existing techniques.

The second chapter (Literature-Related Discovery: Methodology) presents the approach we have developed to overcome these deficiencies/roadblocks and achieve the goal of accelerating discovery. We emphasize the specific improvements made in the discovery generation process.

The next five chapters describe five case studies of potential discovery generated. These include four medical cases (RP, Cataracts, PD, MS) and one non-medical case (WP). Each study includes an ODS LBD approach, and the WP study also includes an ODS LAD approach. In all five cases, large amounts of potential discovery are generated. In four of the cases (Cataracts, PD, MS, WP), this is the first time that potential discovery has been reported using a literature-related approach. In the WP case, this is the first reported non-medical application of an LRD approach. In the RP case, which has become a rite of passage for anyone proposing a new ODS LRD approach, we generate almost two orders of magnitude more potential discovery than anyone else who has reported research on this problem.

Specifically, the third chapter (Literature-Related Discovery: Potential Treatments for Raynaud's Phenomenon) presents the first specific application of our discovery techniques. We addressed the same RP problem that Swanson addressed in his 1986 paper, using the same Medline database.

The fourth chapter (Literature-Related Discovery: Potential Treatments for Cataracts) addresses potential treatments and preventative measures for cataracts. We used the same conceptual approach as for the RP problem, but the specifics of the solution were streamlined compared to the approach for the RP problem, and much less time was required to generate potential discovery. We also implemented the concept of MeSH-based semantic filtering.

The fifth chapter (Literature-Related Discovery: Potential Treatments for Parkinson's Disease) addresses potential treatments and preventive measures for PD. We started from the cataracts problem approach, and made further improvements.

The sixth chapter (Literature-Related Discovery: Potential Treatments for Multiple Sclerosis) addresses potential treatments and preventive measures for MS. We started from the PD problem approach, and made further improvements, especially in our treatment of related literatures.

The seventh chapter (Literature-Related Discovery: Potential Improvements in Water Purification) describes the non-medical problem we addressed: improved water purification techniques. As far as we know from the reported studies, it is the first real LRD application to a non-medical problem. The LAD application to water purification that we report is the first application of LAD of which we are aware.

The final chapter summarizes the lessons learned from each study and from the aggregate. It provides an overview of what has been accomplished with our ODS LRD techniques, and what recommendations we offer for future work.

## **2.0 BACKGROUND**

This section presents a survey of the ODS LBD literature from 1986 to the present.

### **2.1 Leading ODS LBD Techniques**

#### **2.1.1 Swanson's Original Approach - 1986**

ODS LBD originated with the publication of Swanson's 1986 paper on Fish Oil and RP [5]. Swanson was pursuing treatments for RP by examining disparate disciplines for potential solutions - an ODS problem. Swanson linked the Fish Oil literature to the RP literature through intermediate (i.e., biomedical mechanisms) literatures, and published this hypothesized 'discovery'.

Swanson's initial concept matured over a number of years and documents, and continues today. Many subsequent ODS LBD studies were performed by Swanson/ Smalheiser, including migraine and magnesium [9], somatomedin-C and arginine [10], and potential biowarfare agents [11]. They also developed more formalized analytical techniques for hypothesizing discovery; e.g., [12,13]. The main focus of the present subsection will be on the initial 1986 paper [5], since it has served as a model for many future ODS LBD studies, and its principles really haven't changed very much in their incorporation in succeeding ODS LBD studies. His fundamental concept was outlined in the Introduction.

Swanson used two main conditions in the 1986 ODS LBD paper for ranking phrases as potential discovery candidates. Because these conditions have been used in full or part by other ODS LBD research groups, and because we are concerned that their implementation in many studies has overly constrained the identification of potential discoveries, these conditions will be presented verbatim from a later more comprehensive paper [12]:

- a. In Swanson's terminology, C is a "source literature" [migraine, in his example], "B-terms" are "intermediate title words or literatures", and A-words are "title words that can represent promising target literatures". His first main condition states: "Each [A] candidate is then assigned a rank *according to the number of different B-words in the AB-BC co-occurrence linkages in which it participates* ..... This ranking algorithm is based on a presumption that the *greater the number of B-linkages, the greater the chance that some of them will be biologically important.*"
- b. "Each of the remaining B-word candidates is then searched in MEDLINE to determine the total number of titles in which it occurs. Restriction (ii): these words are further screened automatically to *retain only those that occur with greater relative frequency in migraine titles than in titles from MEDLINE as a whole.* The latter frequency is determined from the information displayed in the online search which shows each search



statement and the corresponding number of items found. More specifically, we retain only words for which *the probability is small that a random allocation of words to titles could lead to a number of co-occurrences with “migraine” equal to or greater than the observed number.*”

The first condition assumes the expanded literature can be separated into multiple orthogonal literatures, where each literature addresses a major thrust of the problem being addressed. It then assumes that a word or phrase found in multiple literatures (that categorize the problem of interest) is a higher priority discovery candidate than a word or phrase that was found in a single literature. In other words, the more characteristics of a problem that the word or phrase addressed, the higher the probability it could lead to discovery. For the RP example, if three important thrusts are blood viscosity, platelet aggregation, and vasodilation, then a word or phrase that occurred in all three expanded literatures would rank higher than a word or phrase that occurred in only one literature.

The second condition assumes that the more a word or phrase stands out in an expanded literature relative to background because of its occurrence frequency, the more evidence exists that there is a stronger tie between the word or phrase and the problem, and the more likely the word or phrase is to lead to discovery. Swanson used these two conditions to essentially filter out most of the phrases in the expanded literature, and the discovery phrases he identified were at or near the top of the rankings when these two conditions were applied.

While application of these two conditions reduces the number of candidates to be considered drastically, it is our opinion that real potential discovery is being eliminated also. Further, it is our opinion that these two conditions are completely arbitrary, and there is no reason to expect them to yield discovery in general.

Two simple examples will illustrate why we find these conditions problematical, at least for the RP problem. Suppose there are three main themes for RP: blood viscosity, platelet aggregation, vasoconstriction. Suppose further that, by 2025, treatments have been found for RP, and the optimal treatment is found (hypothetically) to be Vitamin L to reduce blood viscosity, Vitamin M to reduce platelet aggregation, and Vitamin N to reduce vasoconstriction. Then, rather than researchers having looked for one substance that would impact all three main themes, or even two themes,

the optimal trajectory to discovery would have been researchers looking for three separate substances. Only in the case where it was found (hypothetically) in 2025 that the optimal treatment for RP was one substance (to address all three main themes above) would the optimal trajectory to discovery have been researchers applying Swanson's first condition. Thus, unless the optimal treatment was known beforehand, prioritizing a potential discovery candidate by the number of problem characteristics it impacts serves no useful purpose, and overconstrains the solution.

However, we should not underestimate the importance of substances that impact a number of problem characteristics. For example, dehydration (water deficiency) will result in a number of symptoms, and correction of this deficiency will eliminate the symptoms. For this type of causal situation, substances that impact multiple symptoms should certainly receive high consideration. That is a different statement from requiring that number of problem characteristics impacted be imposed as a generic filtering condition.

The second condition of high relative frequency appears counter-intuitive to us, and we believe it leads away from discovery, not towards discovery. Because this condition has appeared ubiquitously in almost every successive ODS LBD study to Swanson's, we will devote some discussion to its consequences at this point.

In our own (and other) studies of the RP problem, one of the highest relative frequency discovery candidates is Fish Oil. It was the central hypothesized discovery of Swanson's initial ODS LBD paper. The high frequency is based on many papers having been written about laboratory experiments and clinical trials that show Fish Oil reduces blood viscosity and platelet aggregation.

Realistically, it is difficult to believe that so many researchers would be involved in these Fish Oil-blood viscosity/platelet aggregation experiments and not one would recognize the link between reducing blood viscosity/platelet aggregation and treating RP.

**In fact, we believe the linkage was essentially recognized in print! We assert that Fish Oil is an incremental discovery at best, and could have been classified as an innovation, even though it has been presented in multiple ODS LBD studies as a discovery for the treatment of RP.**

Starting in the late 1970s, there was an explosion of articles in the medical literature that addressed the antithrombotic and circulatory enhancement effects of fish, fish oil, and constituent fatty acids (e.g., “We suggest that the mechanism behind this reduction was a changed balance between pro- and anti-aggregatory prostaglandins towards the anti-aggregatory side, caused by eicosapentaenoic acid from fish lipids” [14]; “The results suggest that dietary supplementation with fish oil may be beneficial in reducing myocardial damage associated with coronary artery thrombosis” [15]; “The present findings suggest that moderate dietary supplements of fish oil may be beneficial in the prophylactic treatment of ischemic cerebral vascular disease” [16]; “These findings suggest that a diet rich in omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid, will reduce platelet/vessel-wall interaction and may reduce the risk of ischaemic heart disease” [17]; “We conclude that the consumption of as little as one or two fish dishes per week may be of preventive value in relation to coronary heart disease.” [18]). Prior to that time, fish oil articles addressed first the properties of fish oil, and then the impact of fish oil as a food supplement on livestock.

Thus, it was well known by the late 1970s-early 1980s that fish oil and its constituents had a positive impact on thrombotic, atherosclerotic, and other circulatory disorders. In this time frame, at least six articles suggested a link between fish oil or its constituents and vascular diseases.

“Eicosapentaenoic acid and prevention of atherosclerosis” [19]; “This finding suggests that, in vivo, high levels of E.P.A. and low levels of A.A. could lead to an antithrombotic state in which an active P.G.I<sub>3</sub> and a non-active T.X.A<sub>3</sub> are formed. Eskimos have high levels of E.P.A. and low levels of A.A. and they also have a low incidence of myocardial infarction and a tendency to bleed. It is possible that dietary enrichment with E.P.A. will protect against thrombosis” [20]; “Evidence for the mechanism by which eicosapentaenoic acid inhibits human platelet aggregation and secretion - implications for the prevention of vascular disease.” [21]; “Dietary use of a fatty acid like eicosapentaenoic acid (which would be the precursor for a delta17-prostacyclin (PGI<sub>3</sub>) but is transformed by the platelets into nonaggregating thromboxane A<sub>3</sub>) might have beneficial effects as antithrombotic therapies” [22]; “Modification of blood rheology by dietary omega-3 fatty acids is of potential value in the treatment of vascular disease” [23].

Finally, “.... in patients with peripheral arterial disease .... It is concluded that rheological changes that result from a diet rich in eicosapentaenoic acid may contribute to the suggested protective effects of such a diet against arterial disease and that such changes are of potential therapeutic importance in established arterial disease.” [24]. **What more is needed for establishing prior art than the title of Woodcock et al’s paper: “Beneficial effect of fish oil on blood viscosity in peripheral vascular disease”**

While none of these papers mentioned RP specifically, how much of a leap is it from peripheral vascular disease to RP? For example, [25] lists drug therapies for peripheral vascular disease, and presents this information in two categories: intermittent claudication and Raynaud’s Disease. Additionally, most of the hospital Web sites we examined list Raynaud’s Disease under peripheral vascular diseases. Thus, depending on how broadly the core RP literature is defined, Fish Oil may or may not have been a potential discovery. The oversight in the literature appears due more to poor indexing (not adding the Mesh term Raynaud’s Disease to at least some of these articles) and inadequate retrieval (not using synonyms for RP) than the lack of information availability within the medical community.

Therefore, the ‘discovery’ of Fish Oil and Eicosapentaenoic Acid by literature-based techniques is an incremental discovery at best, since the linkages between peripheral vascular disease and Fish Oil had already been shown in openly-published literature. The revolutionary discovery was proposing/ demonstrating the linkage between the ingestion of fish (and/or its constituents) and its positive effects on the circulatory system. While it is difficult to pinpoint a specific discovery date, certainly articles suggesting such a linkage were appearing in the open literature in the late-1970s or before.

These remarks are not meant to denigrate Swanson’s concept. We believe the fundamental concept remains valid, and a major step forward using the literature as a basis for hypothesizing discovery. However, we believe there is an incompatibility between discovery and **extensively reported research in directly related** literatures. We believe discovery will have higher probability if **indirectly related** literatures are accessed, or perhaps **isolated low frequency phenomena** are found in **directly related** literatures. Intuitively, one would expect that output from one or two researchers who

are at least somewhat (and preferably very much) removed from the core literature research would have a better chance of resulting in discovery through a literature-linking mechanism.

Chances are highest that researchers from directly related literatures would be most aware of potential applications of their concepts to RP, and the greater the number of researchers working in these directly related literatures, the higher the probability that at least one researcher would be aware of the core literature problem/ application. As researchers work in literatures related more indirectly to the core, chances are reduced that they would be aware of the core literature problem, and the potential for discovery increases. Unfortunately, as the indirectly related literatures become more remote from the core literature, the number of paths to be traversed increases drastically, raising the complexity of the problem substantially.

Thus, we have the paradox that chances for discovery are probably highest as one proceeds further from the core literature to very indirectly related literatures, but the linkage between the indirectly related literature concept and the core literature problem becomes more difficult to identify as the related literature becomes more indirect. This has profound consequences for the conduct of ODS LBD, since greater distance between the expanded literature and the core literature necessitates greater involvement of technical specialists who understand the linkages among these intermediate steps.

For example, as Swanson implies, a non-specialist could understand papers concluding that Fish Oil reduces blood viscosity, papers concluding that reduced blood viscosity could have a positive effect on RP, and therefore could draw the conclusion that Fish Oil may impact RP positively. However, if the Fish Oil papers described the impact of Fish Oil on the viscosity of synovial fluid in the knee, then it would realistically take a medical expert to draw the link between changes in synovial fluid viscosity and blood viscosity in order to close the loop between Fish Oil and RP.

These two conditions constituted the primary numerical filters used by Swanson to narrow the pool of candidate discovery phrases to more manageable numbers. Either the same, or related, numerical conditions have been used by later researchers for similar filtering purposes. We do not believe these are either necessary or sufficient conditions for discovery. They represent attempts to apply information technology principles to

automation of ODS LBD, but there is no evidence that they are associated with discovery. There is nothing to rule out a discovery word or phrase being associated with a high value of either of these filters, but the same could apply to a non-discovery word or phrase. There is also nothing to rule out a discovery or non-discovery word or phrase being associated with a low value of either of these filters.

Finally, for ‘vetting’ his potential discovery candidates as being independent from the core RP literature, Swanson used a co-citation analysis approach to insure that RP and the potential discovery concept were not being co-cited in the same paper. His approach was highly intensive manually, which probably motivated the need for developing filtering metrics. His database was mainly MEDLINE records published between 1975 and mid-1985. He did not seem to have a formal approach for generating the intermediate ‘B’ literatures.

Most of Swanson’s later work appears to be focused on CDS LBD problems for the medical literature. He and Smalheiser [12] developed a software system called Arrowsmith to simplify use of his CDS LBD approach. Because Arrowsmith could be used in a quasi-open system mode (quasi-ODS), we summarize its operation.

### 2.1.2 Arrowsmith/Smalheiser - 2005

Arrowsmith operation is described in detail in two major references [12,26], and its improved selection of ‘B’ literatures (terms) is described in a more recent paper [27]; we select the 2005 paper for purposes of this review. Arrowsmith presently operates from the MEDLINE database only, and therefore can generate only medical potential discovery. The user initiates Arrowsmith operation by conducting two PubMed searches for literatures ‘C’ and ‘A’. The Arrowsmith software then stems the titles of the papers in each literature, and makes a list of all single, double, and triple word phrases that are found in common in the titles of both literatures. The resulting raw ‘B’ list is then filtered and ranked further before being displayed to the user. The user can then examine ‘A’  $\rightarrow$  ‘B’  $\rightarrow$  ‘C’ list linkages to identify credible paths that show how the solution impacts the problem. While Arrowsmith presently uses titles only, it could be upgraded to include Abstracts. It could also be upgraded to include additional literature links (e.g., ‘A’, ‘B’, ‘C’, ‘D’). Because of the constraints imposed by the requirement for exact phrase matching between the ‘AB’ and ‘BC’

literatures, adding the capability for using synonyms would seem to offer a major step forward as well. In addition, MeSH terms have been integrated into the matching process and the title display. Thus, an upgraded version of Arrowsmith that used Abstracts as well as titles, that included additional literature links, and that employed synonyms would appear to be a very powerful tool for closed systems and quasi-open systems.

There can be many raw phrases on the intermediate ‘B’ list. Therefore, much effort has been expended with Arrowsmith to reduce the number of phrases on the ‘B’ list. Seven filters are listed in [26]. We ran some Arrowsmith experiments in a quasi-open systems mode, using a clustering-based approach to filter the phrases on the ‘B’-list, and our experiences are reported in the MS paper [28].

### 2.1.3 Gordon and Lindsay’s Original Approach - 1996

Gordon and Lindsay [29] used an information technology-based approach to help automate the ODS LBD process. In contrast to Swanson’s use of words from titles as variables, Gordon and Lindsay used words and phrases from full MEDLINE Abstracts as variables. They identified the intermediate ‘B’ literatures through a phrase frequency analysis of the core RP literature and subsequent examination of the high frequency high medical content phrases.

While we have no problem with their use of selecting high frequency phrases for proxy clustering to identify intermediate literatures, we have substantial problems with their use of identifying high frequency phrases as potential discoveries, as they did when finally selecting Fish Oil/Eicosapentaenoic Acid. We have problems for the reasons presented in our discussion of Swanson’s approach. There is no reason a priori that a high frequency phrase should be related to discovery, and much intuitive reason to believe its chances of being a discovery item are reduced.

To summarize, we don’t believe that Gordon and Lindsay replicated Swanson’s result in all its dimensions, and we don’t believe their method has the potential for generating the full scope of discovery possible with a literature-based approach. Their method is a reasonable approach for the important step of identifying the intermediate literatures. See [7] for further details.

### 2.1.4 Weeber - 2001

Weeber et al [30] used a two step model of discovery (ODS step followed by CDS step) to simulate Swanson's actual 'discovery'. They mapped the text into the Unified Medical Language System (UMLS) as a thesaurus, to standardize vocabulary and reduce dimensions substantially. Rather than identify an intermediate literature with no prior knowledge, they started with Swanson's finding of "platelet aggregation, blood viscosity, and vascular reactivity". For each of the three literatures above, they identified potential discovery candidates, using a ranking scheme based on frequency. In fact, their approach emphasized high frequency concepts.

There are a number of problems with this approach. First, it requires a detailed thesaurus for feasibility. While such a thesaurus exists for the medical field, a similar resource is not available for many other fields. Second, it is high frequency-based. We have discussed problems with this requirement for identifying discovery previously. Third, the specific approach presented did not identify the intermediate literatures a priori. Finally, because of where Fish Oil appeared in the rankings, we question whether it would have been noticed easily as a promising discovery concept had the authors not known the answer beforehand, as the authors claim. Their combining an ODS approach with a CDS approach could provide useful insights about linking mechanisms. See [7] for further details. Further, Weeber et al [31] identified potentially new target diseases for the drug thalidomide.

#### 2.1.5 Stegmann and Grohmann - 2003

Stegmann and Grohmann [32] used a co-word clustering of MeSH terms to identify potential discovery by location on density-centrality maps. Examination of the resulting density-centrality map shows interesting terms to be concentrated in the lower left quadrant (i.e., exhibit below-median centrality and density values). This is true for the RP intermediate literature as well as for the Fish Oil literature. However, there are interesting terms in other quadrants as well, and not all terms in the lower left quadrant are interesting. Thus, the merit of this characterization approach is to identify a starting point for exploring discovery rather than a hard roadmap. Intuitively, the lower left quadrant is in line with our previous statements about relatively rare events being more favorable for discovery than high density central events, although unitary events have been excluded.



### 2.2.6 Srinivasan - 2004

Srinivasan [33] generated a potential discovery-identifying algorithm that operates by building MeSH-based profiles from MEDLINE for topics. A profile is a weighted vector of MeSH terms that together represent the corresponding topic. Additionally, MeSH terms are separated by semantic type (the MeSH vocabulary has already been classified using 134 Unified Medical Language System [UMLS] semantic types), and weights for each MeSH term are computed within the context of a semantic type. The authors use term frequency-inverse document frequency (TF-IDF) weighting and then normalize the weights.

Srinivasan's ODS LBD algorithm operates as follows. First, a MeSH profile is built for the initiating 'C' topic of interest (in the medical context, 'C' could be a disease for which a treatment is desired, or a substance for which potential target diseases are desired). MeSH terms in the profile have TF-IDF weights that are normalized within each semantic type. A select number of 'B' MeSH terms ('B' represents the intermediate literature that links the initiating literature 'C' with the target literature 'A') are automatically selected from the user specified semantic type (ST) 'B' vector components and their profiles are built. These are then merged to form a final profile. The combined weight of a term is the sum of its weights in the individual 'B' profiles. In the last step, the 'A' MeSH terms are limited to those representing novel connections. An 'A' MeSH term's score is regarded as the system derived estimate of the potential value in its association with the 'C' topic. This score depends both on the number of paths connecting back to 'C' as well as the strengths of these paths. The higher the score, the stronger the recommendation made by the system. The 'A' MeSH terms within each semantic type are ranked by combined weight.

In the initial paper [33] and subsequent publications [34,35], using the technique above, the authors start with curcumin and look for ailments this substance could potentially benefit. Three ailments identified are "retinal pathologies including diabetic retinopathies, ocular inflammation and glaucoma", Crohn's Disease /Ulcerative Colitis (both members of Irritable Bowel Syndrome), and EAE/Multiple Sclerosis.

We subjected these potential discoveries to two of the four vetting steps that we employ for our own potential discovery candidates: 1) check for prior art in the mainline core journal literature (MEDLINE, SCI); 2) check for prior

art in the core patents literature. Our check of the core literature, including text and MeSH query terms, showed that prior papers and patents contained the connections between curcumin and the three diseases mentioned, and, based on our vetting criteria, there was neither discovery nor innovation present [7,8].

Use of MeSH terms for identifying potential discovery is a double-edged sword. Because of the finite number of MeSH terms present, the dimensionality is reduced substantially. However, the breadth of coverage of each variable (MeSH term) is increased substantially (going from text to MeSH), and each MeSH term can represent many text terms. This becomes important in the vetting step, where many of the text terms (represented by the MeSH term) can be used for the purpose of refuting discovery (establishing prior art). In other words, gains realized in the front-end through reduced dimensionality may be lost in the back-end vetting step.

The technique may have some potential for identifying discovery, but because of its operation in MeSH space, more attention needs to be paid to proper vetting of any potential discovery candidates.

#### 2.2.7 Yildiz and Pratt - 2006

Yildiz and Pratt [36] use an ODS LBD system called LitLinker that incorporated knowledge-based methodologies with a statistical method. The literature-based discovery begins with a starting term (the ‘C’ literature), then uses a text mining process to find a set of terms (linking terms – the ‘B’ literature) that are directly correlated with the starting term, and uses the same text mining process to identify a set of terms that are correlated with each linking term. Finally, Litlinker ranks the target terms by the number of linking terms that connect the target term to the starting term.

In searching the database, Litlinker uses MeSH terms as the representation of the content of the documents and performs searches on them to collect the literatures. To find correlations, Litlinker calculates the probability of a term appearing in a literature by dividing the number of documents of the literature in which the term appeared by the total number of documents in the literature. Those terms with distances between the probability of a MeSH term in a specific literature and the general distribution of this MeSH term in the background set of literatures larger than a pre-defined threshold are marked as the correlated terms to the starting or linking term.

Yildiz and Pratt [36] reported potential discovery results for three cases: Alzheimer's Disease, Migraine, and Schizophrenia. They used precision and recall as key evaluation metrics. The authors list one detailed example for each disease, and provide statistics for the remainder of the potential 'discoveries'. Our check of each of the three detailed examples showed prior publications and patents for each case [8], and the projections could not be classified as discovery or innovation.

In response to [8], Yildiz and Pratt [37] have questioned our use of the patent literature examination vetting step as being overly harsh. Most of the potential 'discoveries' reported by previous ODS LBD researchers (such as Srinivasan) were Medline-based (since all the previous topics examined were medical), with perhaps some potential 'discoveries' coming from SCI supplementation. Their search techniques did not access the patent literature; why, then, should the patent literature be used in the vetting process?

We take the definition of discovery literally. We work on the assumption that every potential discovery we report in the literature could be patentable (or its equivalent in uniqueness), if we so choose. To be patentable, a potential discovery derived from ODS LBD has to meet three main conditions: no prior art; value added by the linkage; sufficiently important to justify the resource expenditures required to patent. These conditions are not a function of the databases we selected. From our perspective, claiming discovery based on no prior art from MEDLINE search only, or SCI search only, or patents search only, or search of any other restricted database, is of limited practical consequence. If Yildiz and Pratt, and other ODS LBD researchers who claimed potential discovery, had presented their results as "no prior art based on Medline search only", we would have much less of a problem, since, in those cases in which this 'no prior art' condition held, that is a factual statement. However, ***when there is an equivalence drawn between 'no prior art in Medline' and potential discovery, we have problems with such claims.***

In vetting the results of our own ODS LBD studies, we were much harsher than in the vetting we report in this background section. Most of the findings of prior art (during the vetting of our own studies) occurred in the patent literature vetting step. Had we performed the core journal literature vetting steps only (Medline and the SCI), we would have had substantially

more potential ‘discoveries’. However, we believe that presenting such results as potential ‘discoveries’ to independent third parties would have impacted the credibility of our findings, and would have cast doubt on the credibility of our whole approach. Therefore, *we defined discovery in the sense in which it is understood by most of the technical community*, and designed our vetting process to support that goal.

As was the case with Srinivasan’s method, the Yildiz-Pratt technique may have some potential for identifying discovery, but because of its operation in MeSH space, more attention needs to be paid to proper vetting of any potential discovery candidates.

#### 2.1.8 van der Eijk - 2004

This approach [38] is based on mapping from a co-occurrence graph to an Associative Concept Space (ACS), where concepts are assigned a position in space such that the stronger the relationship between concepts, the closer they lie in the ACS. Potential discovery can then be obtained from strong implicit relationships, where concepts are close to each other in ACS but have no direct connections.

The text words are first transformed to concepts through use of a thesaurus, in this case the MeSH terms of MEDLINE. A list of a document’s concepts is called a concept fingerprint of that document. For each identified concept, a unique concept identifier is added to the fingerprint. The concept identifier is assigned a relevance score, based on term frequency and the specificity of the term in the thesaurus. The fingerprints form compact representations of documents, because they are lists of concept identifiers.

Co-occurrence of concepts in fingerprints is a central metric. Concepts are mapped into an ACS. Concepts that are connected by frequent co-occurrence paths, either directly or indirectly, should have a small distance in the ACS, while concepts with few or no paths between them should be far apart. A Hebbian learning algorithm is used to determine an appropriate position for the concepts. As a result, the Euclidean distance between two concepts is a measure of both co-occurrence and how many co-occurring concepts the two concepts have in common. Thus, co-occurrence quantity is a driving metric of relative positioning in ACS.

Two examples of potential discovery are provided. We checked the first example (relation between macular degeneration and deafness) and found substantial prior art in the mainstream research literature [7]. We then checked the second example (relation between insulin and ferritin). While there was no directly connected prior art in the literature, we believe the relation would have been obvious to any researcher [7], and thus there appeared to be no value added. We don't view the projections as discovery or innovation.

#### 2.1.9 Gordon and Dumais - 1998

Gordon and Dumais [39] used an alternative approach to Gordon's previous discovery work. They used latent semantic indexing (LSI), based on higher-order co-occurrences, to compute document and term similarity. This approach allows articles to be accessed, without exact term matching, as long as they have semantic similarities. Similar to factor analysis of phrases, where variables are transformed from phrases to more general factors, LSI transforms phrases to more general factors, or concepts, resulting in a lower dimensional space. The terms and documents can now be expressed as a vector of statistically independent factors in the lower dimensional space. The closeness of any two terms can be estimated by the cosine of their vector expressions.

Gordon and Dumais hypothesized numbers of potential 'discoveries'. All the discoveries identified occurred with high frequency in the literature of interest, and all were drugs developed to treat the intermediate mechanisms (e.g., high blood viscosity, high clotting, vasoconstriction). Drugs that were developed to reduce blood viscosity and clotting, and are now being proposed to apply to RP, are not our idea of discovery! At best, they could be viewed as potential innovation. Use of LSI for ODS LBD offers the possibility of linking literatures with similar concepts but very different terminology, thereby leading to potentially radical discovery. We don't believe the potential was realized in the study reviewed. See [7] for further details.

#### 2.2.10 Bruza – 2004-2006

Bruza and co-workers [40-43] have generated a semantic space approach that bears some similarities to LSI. It is based on the Hyperspace Analogue to Language (HAL) model, which produces representations of words in a

high dimensional space that seem to correlate with the equivalent human representations.

HAL takes a corpus of text as input and learns a representation of words by accumulating weighted associations of co-occurring words in the context of a fixed length window. More specifically, given a vocabulary of  $n$  words drawn from the corpus in question, HAL computes an  $n \times n$  matrix by moving a window of length  $l$  over the corpus by one word increments, ignoring punctuation, sentence, and paragraph boundaries. All words within the window are considered as co-occurring with strength 1. When the counts of the sliding window are aggregated, the strength of association between words becomes proportional to the distance between the words, because words that are closer together co-occur in more windows. The row and column in the HAL matrix corresponding to a given word  $i$  are added together to produce a single vector representation for that word. Thus, the vector representation of a word will be a function of the number of times component words appear in the total corpus (word frequency) and how closely the component words are spaced to the word being represented.

Once this semantic space (the HAL matrix) is generated, then discovery is possible by finding strong associations between a 'c' vector (e.g., RP) and potential 'a' vectors (e.g., Fish Oil). Bruza applied his technique to the RP problem, with somewhat inconsistent results. Because of our previously-stated concerns about the degree of discovery Fish Oil has relative to the RP problem, we would need to see further applications of Bruza et al's techniques to problems not addressed previously by ODS LBD before commenting on the efficacy of his approach. However, his philosophy of using weights to increase the importance of low frequency phrases is certainly a step in the right direction.

#### 2.2.11 Wren - 2004

Wren et al [44] used the standard 'A', 'B', 'C' Swanson literature relationship structure for generating potential discovery. He defined classes of objects (e.g., genes, diseases, chemical compounds, etc), extracted class members from a variety of source databases, and then studied their co-occurrences in MEDLINE records (titles and Abstracts) to generate implicit relationships. He prioritized these implicit relationships by comparing actual occurrences in a literature network against a random network model

to evaluate how statistically exceptional is any given set of shared relationships.

An essential component of Wren's approach is the ranking scheme used to prioritize implicit relationships. The relatedness or strength of relationship between two objects is defined as the number of times that the two objects have been co-mentioned (co-occurrence frequency) and the probability that each co-mention represents a non-trivial relationship. Obtaining co-occurrence frequencies is straight-forward; estimating probability of a non-trivial relationship is much more subjective and difficult. Wren estimates the latter by tracking the persistence of MEDLINE relationships over time. If a relationship is observed before a specified date, and observed very infrequently after that, it is assumed to be non-important, and down-weighted accordingly. Thus, the key element to his ranking scheme is co-occurrence frequency and importance.

He proposed the drug chlorpromazine (CPZ) as a potential treatment for cardiac hypertrophy. While there was no firm prior art, we found that CPZ is an anti-psychotic, with many adverse side effects, including adverse cardiac effects. We checked with two cardiac hypertrophy experts, who saw no reason to pursue CPZ for cardiac hypertrophy. See [7] for further details.

In our view, this illustrates the problem with using quantity-based measures to associate with quality judgments (discovery). It also follows from our initial ODS LBD definition, stating more is required than identifying new linkages. There may be valid reasons for the absence of linkages.

#### 2.2.12 Hristovski – 2004

This research group [45] uses semantic predications to enhance co-occurrence-based LBD systems. The predications are produced by the combined application of two natural language processing systems coupled with an LBD system BITOLA.

BITOLA is based on Swanson's original approach, with notable differences. BITOLA uses MeSH terms instead of title words, and uses association rules to relate medical concepts instead of word frequencies. Concept co-occurrence is used to indicate relations between concepts. If 'C' is a starting concept (e.g., a disease for which treatments are desired), then its co-occurrences with all concepts 'B' are found ('B', the intermediate concepts,

could be pathological functions, symptoms, etc), followed by all co-occurrences of ‘A’ (potential treatments) with each ‘B’. The possible number of ‘C’  $\rightarrow$  ‘A’ combinations can be extremely large, as is the case with all the techniques examined in this review.

To reduce the number of combinations to manageable size, BITOLA incorporates filtering and ordering capabilities. The ‘B’ and ‘A’ concepts can be limited by semantic types, and thresholds can be placed on the association rules. To exploit semantic predications in LBD, the method introduces the notion of discovery patterns, which contain a set of conditions to be satisfied for the discovery of new relations between concepts. While the approach makes use of additional information through the associations, it is still fundamentally a co-occurrence-based concept, with all the deficiencies mentioned previously. Rare events that could lead to radical discovery would get low prioritization, and well-known relations would predominate. At best, this approach would be expected to provide a very incremental amount of potential discovery.

Huntington Disease (HD) was used as a test case for discovery. Because of similarities of HD with diabetes mellitus, especially reduced levels of insulin, the authors suggest insulin treatment might be an interesting drug for HD.

This example confirms the concerns we stated relative to high frequency phenomena, and crystallizes the problems with depending on high frequency correlations. The relationship between insulin and HD was obvious to us after reading some of the HD literature, and was certainly obvious to the HD researchers. There were some papers where HD was induced in mice, they developed diabetes, and then insulin was used to treat the diabetes. If insulin had any impact on the HD, surely the researchers would have noticed!

We contacted an expert in HD research, and were told that “the diabetes in early HD is not type 1 diabetes, but is due to insulin release problems rather than an insulin insufficiency....I do not think that treating HD patients with insulin is a good option, unless they are insulin-dependent diabetics”.... The key point here is that if two literatures are disjoint, there may be multiple reasons. It could mean that their union would produce real discovery, and no one had thought of linking them previously. Or, it could mean that their union had been considered previously, and researchers concluded that there was nothing to be gained by the linkage. See [7] for more details.



## SUMMARY AND CONCLUSIONS

First, of the ODS LRD concepts that we have examined in detail, and the many other documents we reviewed but did not address in the present chapter, we believe that most, if not all, of the concepts have not generated discovery in the sense defined in the Introduction. Some of the concepts may have generated innovation. Any discovery that might have emerged would be extremely incremental at best.

We believe the approaches and assumptions made by the majority of the researchers reviewed militate against discovery, and drive the results toward innovation. Almost all the techniques aim for identifying discovery in the 'BC' literature defined previously, which we view as being directly related to the starting 'AB' literature. Most of the techniques are based on correlation and/or co-occurrence phenomena, which are excellent for characterizing a literature, but are problematic for identifying discovery.

High occurrence or co-occurrence frequencies are required for such approaches. This translates pragmatically into many researchers working on a technique in the 'AB' literature. The high frequency approaches therefore assume that none of these relatively large numbers of researchers in the 'AB' target literature would be aware of the applications in the directly related 'BC' literature. We believe such an assumption is unrealistic for the directly related literatures, and our belief is validated by the lack of any discovery in these papers. We believe the very lowest frequency concepts would have the highest probability for potential discovery in the directly related literatures, and these rare concepts are effectively excluded by the high frequency-based techniques. As we proceed to the more indirectly-related literatures (for example, if we have an 'A'-'B'-'C'-'D'-'E' system, where 'D' and 'E' literatures are related more indirectly to the starting 'A' literature), we believe that use of the higher frequency techniques may be somewhat more realistic for identifying discovery, although low frequency phenomena still offer a higher probability that knowledge of the starting literature would be unknown to researchers in the proposed 'discovery' literature. We do recognize that the higher frequency concepts have a stronger evidentiary base than the lower frequency concepts, which may bode well for their nomination as innovations.

Additionally, and along the same lines, the ranking metrics also tend to be frequency-based. Two are commonly used: 1) the frequency of a proposed ‘discovery’ concept in the literature sub-set of interest (e.g., the frequency of occurrence of ‘Fish Oil’ in the Blood Viscosity literature) is required to be much higher than the frequency of this proposed ‘discovery’ concept in the overall source database (e.g., MEDLINE in the Raynaud’s example), and 2) the larger the number of paths between the ‘BC’ and ‘AB’ literatures, the higher the ranking (e.g., the more mechanisms by which Fish Oil can impact the major characteristics of RP) of the proposed ‘discovery’ concept. We believe there is no scientific basis for such ranking metrics, and their use militates against the more infrequent concepts that could represent discovery.

Finally, many of the more recent approaches use the MeSH variables in place of text variables. While MeSH has certain advantages, such as a lower-dimensional space and the ability to include concepts that may not be represented by specific words or phrases in text, it has some glaring disadvantages. Very recent MEDLINE articles are not yet indexed in MEDLINE, and therefore will not be accessed by a purely MeSH-based query. Also, the indexers make mistakes, and do not include all the MeSH terms that should be included in an indexing. Potential discoveries will not appear, because they could not be accessed by a purely MeSH-based query. Finally, in the vetting process, the breadth of MeSH terms opens the door to the use of many proxy terms for generating prior art and thereby refuting potential discovery.

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## **Chapter 2 - LITERATURE-RELATED DISCOVERY: METHODOLOGY**

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### **1.0 A Systematic Approach for Accelerating Discovery and Innovation**

#### **1.1 Process Requirements for Discovery**

The purpose of this chapter is to identify characteristics of potential discovery, and to present a generic approach for targeting potential discovery. Equally important, as demonstrated by some of the problems in the Background section of Chapter 1 (also see [1]), a vetting approach is described that insures verification of claimed potential discovery.

All LBD/LAD types share the common feature that more than one literature is required to address the problem of interest. If only one literature were required, then the solution would have been discovered by the producers and readers of that literature. What properties should these multiple literatures have for credible LBD/LAD?

- All the literatures contributing toward the solution of the problem should be complementary. Each literature should contain unique information that contributes to the total problem solution, and without each literature's unique contribution the overall problem cannot be solved.
- All the literatures should be disjoint. Otherwise, an individual's or group's knowledge of all literatures would eliminate literature-based discovery, since the information contributing to the solution could be pieced together by one individual.
- All these literatures should be as comprehensive as possible; otherwise, the disjoint-ness assumption may be a consequence of the limited literature selected, and may not be valid.
- All these literatures with unique information must be linked to form a whole that is greater than the sum of its parts.

The first author's text mining efforts over the past decade have been focused on developing methods to systematically access external sources of



information that could contribute to problem solving for specific technical disciplines, technologies, systems, operations, or technical problems in general. Our group has applied text mining to assessing the technical structure and infrastructure of 1) single technologies [e.g., nanotechnology, anthrax] [2,3] and 2) country portfolios of myriad technologies [China-India] [4-7]. These methods have been integrated with the discovery literature characteristics above to form a systematic approach for accelerating discovery.

In particular, we have developed a generic approach to systematic acceleration of ODS LRD, and have applied six variants of this approach (mainly ODS LBD variants) to five problems: four medical (RP, cataracts, PD, MS) and one physical science (WP). After summarizing the generic approach, we will proceed in succeeding papers to the details of the approach and the potential discoveries made on the five problems.

## 1.2. Summary of Generic Approach To ODS LRD

### 1. Retrieve Core Literature of Target Problem

- Generate query for core literature
- Enter query into database search engine and retrieve core literature

### 2. Characterize Core Literature

- Obtain technical infrastructure of core literature (key researchers, Centers of Excellence) through bibliometrics
- Obtain technical structure of core literature (pervasive thrusts, relationships among thrusts) through computational linguistics. Specifically, cluster core literature records to identify key technical thrust areas that characterize the core literature

### 3. Expand Core Literature

- Generalize query (e.g., for water purification problem, generalize “water purification” as query term to “purification” as query term) for each of the core literature thrust areas obtained in the computational linguistics (clustering) step above
- Identify and retrieve literatures related directly and indirectly to each core literature thrust area, to insure that potential discovery will impact all the major thrust areas that characterize the core literature

### 4. Generate Potential Discovery

- Restrict classes of solutions. For example, in the RP problem, restrict solutions to non-drugs.

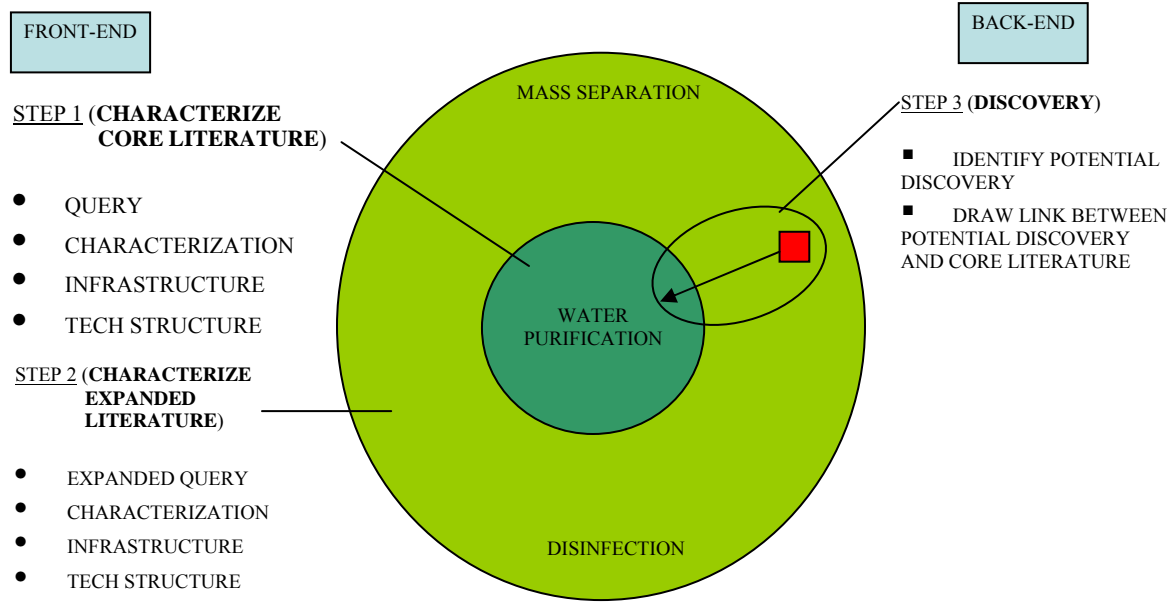
- Examine all records in expanded literature that fall within the restricted classes.
- For records that appear to contain potential discovery, perform vetting procedure as described later.

At this point, two general paths can be followed. In ODS LBD, the expanded literature is analyzed by different means for potential discovery candidates. The examples in this monograph will show six different, yet related, analytical approaches used successfully. In ODS LAD, the authors of the expanded literature are used to generate potential discovery candidates. The examples in this monograph will include one approach for ODS LAD.

### 1.3. Outline of Generic Approach to ODS LRD

We now proceed to examine the generic approach details further. Figure 1 contains a schematic of our generic text mining approach to ODS LRD. The inner circle represents the core literature of the problem to be solved. In the example for Figure 1, the problem to be solved is identifying ‘improved’ alternatives to existing water purification technologies, where ‘improved’ could encompass any combination of lower cost, lower energy use, lower maintenance, higher reliability, lighter weight, and improved modularity for field assembly. Thus, the core literature is the existing (more or less commonly accepted) water purification literature. The annular region between the inner and outer circles represents literatures related directly and indirectly to the core literature.

Figure 1



The discovery process presented in the present paper is divided into two components, a front-end and a back-end.

### 1.3.1. Front-End

#### Step 1

The front-end component (summarized to the left of the figure) contains two major steps: characterization of the core literature (Step 1) and characterization of the expanded literature, including identification of technical experts associated with this literature (Step 2). In Step 1, a query to retrieve the core literature is developed iteratively [8]. Once the core literature has been retrieved with this query, it is subject to text mining [9]. Bibliometrics provides the technical infrastructure (key authors/ institutions/ countries/ journals, etc) of the core literature, e.g., [2], and computational linguistics (typically, some document and/or phrase clustering mechanism) provides the technical structure (technical thrusts, hierarchical taxonomies) of the core literature, e.g., [9]. Step 1 reflects the scope of many of our mono-technology text mining studies to date.

The criticality of Step 1 cannot be overemphasized. The core literature represents the starting point for the expansion processes. The derived expanded literature determines the pool of discovery candidates. Any gaps in the core literature will be reflected as gaps in the pool of potential

discovery candidates. Therefore, it is imperative that the core literature be as complete and comprehensive as possible for the discovery application.

In addition, for core literature retrieval, extensive exploitation of co-occurrence phenomena across many attributes should be made. For discovery purposes in particular, techniques that specifically exploit the underlying semantic structure of the core literature should also be used, in addition to strictly co-occurrence techniques. The first author has made extensive use of factor analysis in understanding the semantic/conceptual structure of retrieved literatures, and has made less formal use of factor analysis for query refinement of the core literature. The factor matrix filtering technique [10] was developed to exploit the underlying semantic structure of a retrieved literature for the purpose of identifying high technical content phrases based on the strength of their contribution to semantic concepts. This is another approach for selecting new query terms.

We have also made extensive use of citations for identifying additional relevant records. If a relevant record has been identified by, for example, the keyword approach, then the following may be explored to identify additional relevant records:

- A. Documents in the References section of the relevant record
- B. Documents that cite the relevant record
- C. Documents that share one or more References with the relevant record
- D. Documents in the References section of the new relevant records identified in A, B, and/or C.
- E. Documents that cite the new relevant records identified in A, B, and/or C.
- F. Documents that share one or more References with the new relevant records identified in A, B, and/or C.

So far, our focus has been on items A, B, and C. For future studies, we plan to incorporate items D, E, and F.

One of the major differences between our techniques and those of other ODS LBD researchers is the size and scope of our core literature query. Some of our queries contain hundreds of terms, especially those for non-medical topics (because of the MeSH controlled vocabulary in the Medline

database, medical core literature queries can be very short). We strongly believe that the most sophisticated analyses cannot compensate for incomplete data, and strive to make our retrievals as complete and comprehensive as possible.

Some of the more formal techniques (such as latent semantic indexing (LSI) [11,12]) that exploit the semantic structure should also be examined for core literature definition. It remains to be demonstrated in practice whether these techniques that exploit semantic structures offer more capabilities than properly conducted attribute co-occurrence techniques, e.g., [13].

The first author has also proposed latent feature indexing (LFI), of which LSI is a special case, for retrieving additional relevant records. In LFI, many of the bibliometric field features (e.g., authors, institutions, countries, citations) can be substituted for the words or phrases in LSI, and the mathematical operations remain the same. Probably the most promising for enhanced relevant record retrieval is latent citation indexing (LCI), where references are used as features and substituted for words or phrases in the LSI algorithms.

A multitude of information retrieval techniques have been examined for more than a decade at the TREC conferences [<http://trec.nist.gov/pubs.html>], and the interested reader is advised to examine the proceedings of these conferences for the state-of-the-art in information retrieval approaches.

## Step 2

In Step 2, the query developed in Step 1 is generalized and expanded, again iteratively. This expanded query will retrieve records from literatures related directly and indirectly to the core literature. Insights and principles from these disparate literatures/technical disciplines can be extrapolated to solve problems of the core literature. ***To insure that all the major themes in the core literature are addressed in the expansion process, the core literature is clustered to identify these themes.*** We have used a variety of approaches for the clustering, including document clustering, auto- and cross-correlation mapping of words/ phrases, factor matrix analysis of words/ phrases, and manual assignment of words/phrases/records to clusters. This is another major difference between our work and that of other ODS LBD researchers. **Clustering insures that all thrusts will be represented**

**in the expanded literature.** We don't know anyone who has reported the use of clustering to identify the intermediate literature thrusts.

Thus, in the example on Figure 1, the core water purification literature query is expanded to cover/retrieve all of mass separation and disinfection documents. Insights from very disparate mass separation and disinfection approaches can then be extrapolated to solve problems in water purification. Details on query expansion can be found in [13].

### **1.3.2. Back-End**

The back-end component contains the discovery step, which itself contains two sub-components. The first sub-component is identification of potential discovery candidates from the expanded literature, and the second sub-component is drawing the linkages between the potential discovery candidates and the core literature. Ordinarily, ODS LBD researchers apply numerical filters at this point, to reduce the number of concepts that have to be examined for potential discovery linkages. We differ from the remainder of the ODS LBD research community in that **we do not use numerical filters to reduce the number of records that have to be examined.**

Recently, in our newly-developed streamlined medical studies approaches, we have been using two types of **semantic filters** for the medical studies, where the MeSH taxonomy in MEDLINE allows semantic classes to be defined. We restrict potential solutions to selected semantic classes (e.g., potential treatments are non-drug only), and use query term combinations (mainly of MeSH terms) characteristic of prior discovery in the semantic class (e.g., non-drug treatments in the core literature). **We believe these semantic filters are inherently superior to the numerical filters for potential discovery selection and identification!!!**

As will be shown in this section, there are many ways to identify potential discovery candidates, and to draw the subsequent linkages. These techniques differ mainly by the approach mechanics and the types of people used to identify the discovery and innovation candidates. The two main discovery approach types (Literature-Based, Literature-Assisted) are described now.

#### **1.3.2.1. ODS Literature-Based Discovery**

ODS LBD is based strictly on analysis of literatures related directly and indirectly to the core literature. ODS LBD is useful in the planning and concept identification phases of the science and technology (S&T) development cycle. The literature-based approach can be viewed as a very sophisticated type of literature survey, and represents a somewhat different way of doing business for most S&T sponsoring agencies, researchers, and technical journals. **Done properly, ODS LBD has the potential of generating orders of magnitude more discovery than what has been reported so far in the ODS LBD literature (as this monograph will demonstrate).**

#### 1.3.2.2. ODS Literature-Assisted Discovery

We can identify technical experts associated with the ‘external’ directly and indirectly-related disciplines, and then have them focus their expertise on solving problems of interest from the ‘internal’ disciplines. Assembling of experts from multiple disciplines connected to a target discipline of interest could be done through workshops, panels, solicitation of proposals from various disciplines, etc. This literature-assisted people-based approach could easily be incorporated into most S&T sponsoring agencies’ existing operational procedures.

However, in some applications, proper handling of the infusion of large numbers of concepts and insights from disparate disciplines will acquire the characteristics of ‘disruptive technologies’. For example, in the use of ODS LAD to broaden the solicitation of proposals from disparate disciplines, a large number of reviewers may be required to handle the increased volume of proposals, and many of these reviewers will need to be from disparate disciplines.

Thus, the differences between paths ODS LBD and ODS LAD above are in the ‘back-end’, in 1) how the linkages between the ‘external’ and ‘internal’ disciplines are made, and 2) who makes the linkages.

The ultimate goal should be incorporation of both approaches in parallel, to exploit the strengths of each approach while eliminating the weaknesses. This synergy would provide the comprehensiveness and objectivity of the people-assisted literature-based approach coupled with the interaction and feedback of the literature-assisted people-based approach [14].

## 1.4 Details of Generic Approach to ODS LBD

Figure 2 is a flow chart that describes a comprehensive process for generating medical ODS LBD. Because of resource limitations, none of our completed medical studies used the full process, although the MS study came closest. This did not present a problem in practice, since for all topics studied a large amount of potential discovery was generated. For the demonstration-type studies in this monograph, the potential discovery generated was more than adequate for all cases. We will describe the steps in the flow chart, and identify those that were used in each study. The steps on Figure 2 have been numbered for ease of presentation.

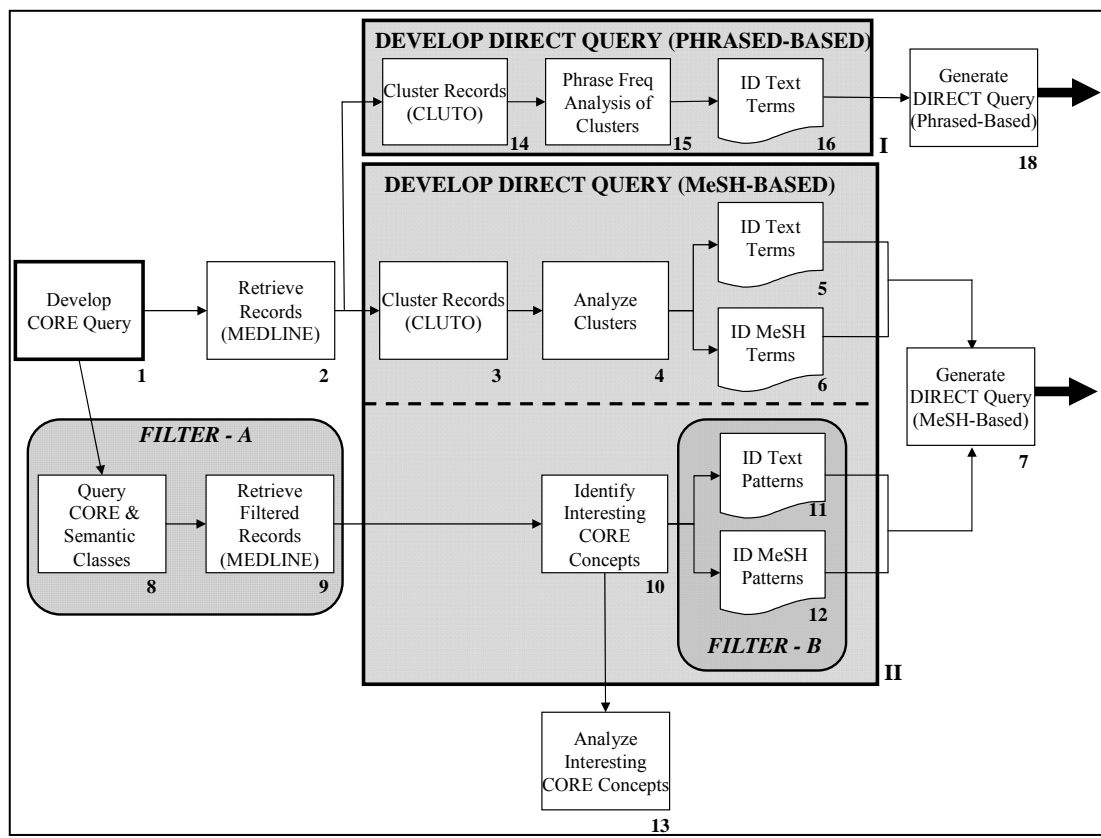
### 1.4.1 Description of General Medical Studies Approach

The implementation of the process for retrieving the core and expanded literatures portrayed schematically in Figure 1 consisted of three steps. In the first step, a core literature was retrieved. In the second step, this core literature was clustered, and was expanded to generate a literature directly related to, but disjoint from, the core literature. In the third step, the directly related literature was expanded to generate a literature indirectly related to, and disjoint from, the core literature, as well as disjoint from the directly related literature.

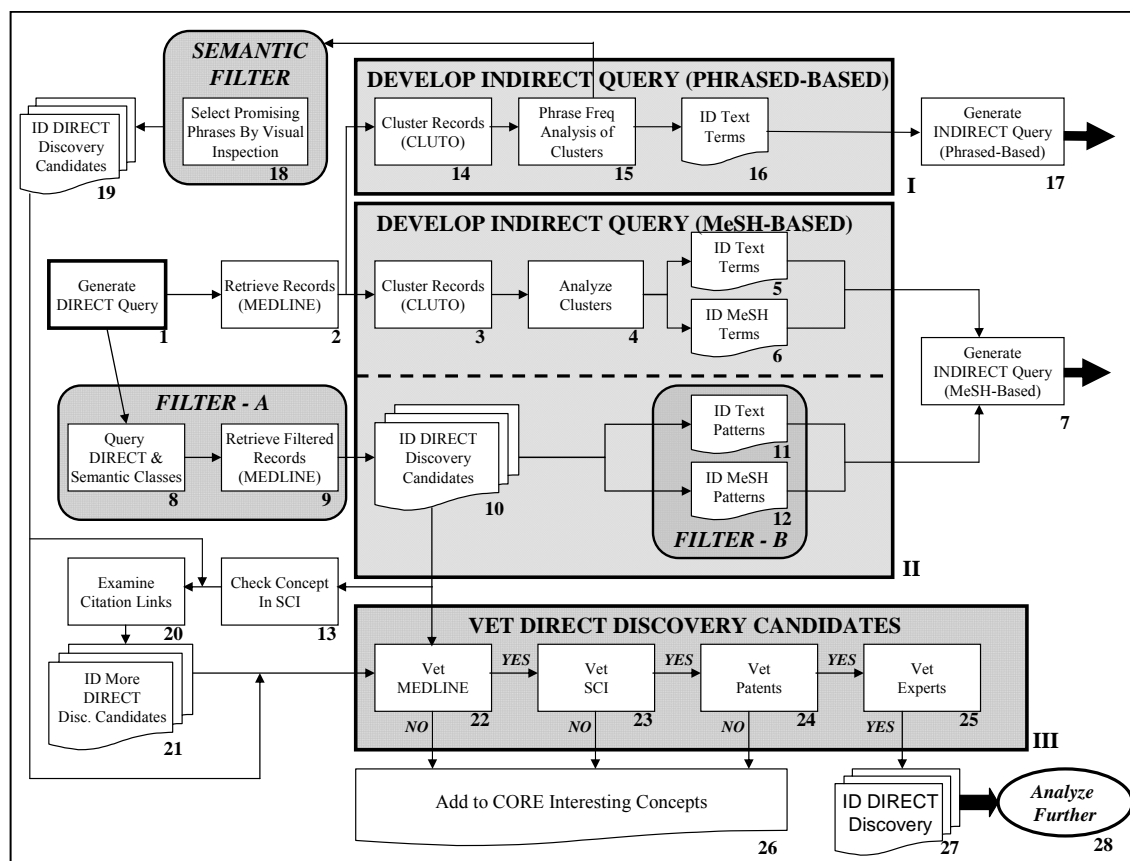
Figure 2 describes the total process in more detail, and consists of three frames. The first frame starts with the development of a core literature query, describes the development of a directly related literature query and the identification of interesting core literature concepts (potential treatments for the medical problem of interest already identified), and ends with the generation of the directly related literature query. The second frame describes the development of an indirectly related literature query and the identification of potential discovery from the directly related literature, and ends with the generation of the indirectly related literature query. The third frame describes the identification of potential discovery from the indirectly related literature. Each frame has its own numbering system.



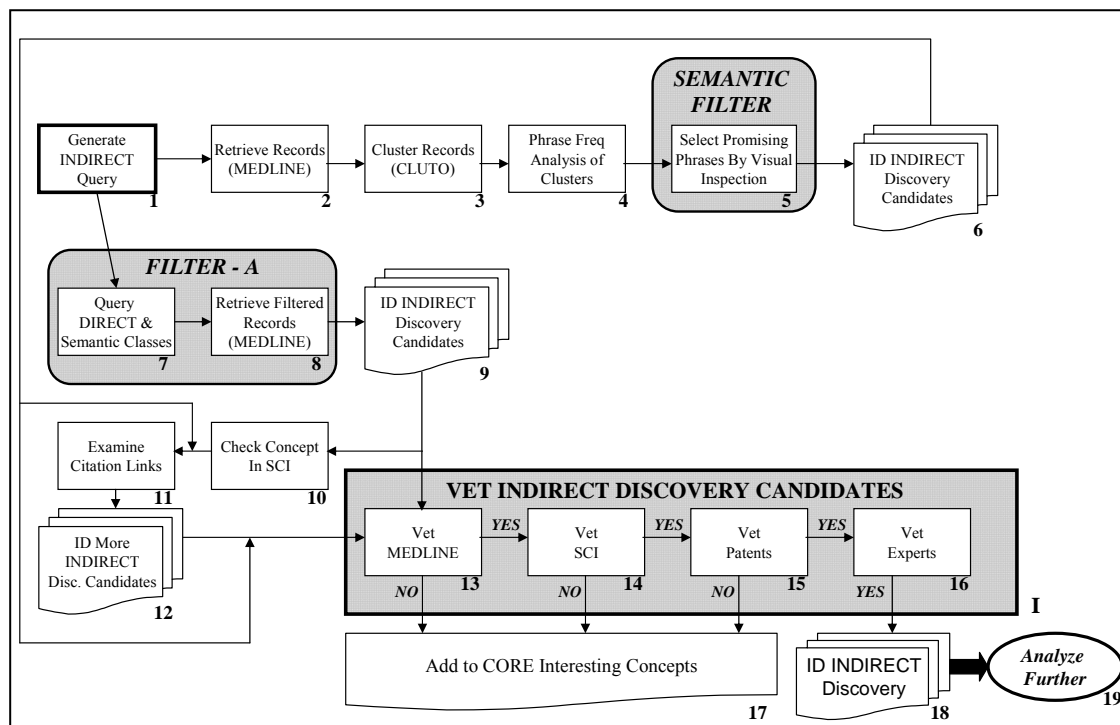
FIGURE 2 – MEDICAL DISCOVERY PROCESS FLOW CHART



FRAME 1



FRAME 2



## FRAME 3

### 1.4.1.1 Frame 1

#### Development of the directly related literature query

In Frame 1, Step 1 is development of the core query. It is based on a review of the background material for the medical topic being addressed, and discussions with experts in the medical topic. In all cases studied, the core queries were extremely simple, due to the existence of the MeSH terms. A single MeSH term tended to cover the core literature. Use of 'cataract\*', for example, covered both its use as a MeSH term and as a text term, and tended to retrieve the total core cataracts literature.

Step 2 is use of the query in the appropriate database search engine for a selected time frame to retrieve records for analysis. Medline was used as the

main database for all studies, although the Science Citation Index (SCI) [15] was used at later stages for expanding discovery through the use of citation linkages.

Step 3 is grouping of the core literature concepts to identify the main medical thrusts, and insure these thrusts are represented in the expansion of the query for retrieving directly related literatures. Document clustering was used as the main core literature grouping technique, where documents are segregated into groups based on text similarity. The CLUTO software package [16] was used for document clustering. In some of the later studies, other core literature concept grouping techniques were used as supplements to the document clustering, including phrase autocorrelation mapping and factor matrix analyses.

Step 4 was analysis of the clusters, or groups obtained by other approaches. The main theme of each group was generated, and the key phrases within each group were identified. Additionally, only groups that focused on biomedical mechanisms and phenomena were selected for the final query expansion, since the potential treatments were focused on impacting these mechanisms and phenomena.

Step 5 was identification of the important text terms in the Abstracts, and Step 6 was identification of key MeSH terms. These first six steps constitute one of the two inputs in determining the directly related literature query. The next six steps constitute the second input in determining the directly related literature query (as well as identifying interesting core literature concepts).

#### Identification of interesting core concepts

Steps 8 and 9 represent the application of the first semantic filter. The purpose is to extract the sub-set of core records that have pre-determined desired characteristics that we would like to see in potential discoveries. In the present group of medical studies, the classes of potential solutions were restricted to non-drug approaches, and these classes were defined (for the last three medical studies) by selection of appropriate MeSH terms that represented non-drug approaches (e.g., medicinal plants, phytotherapy, etc). In future studies, the classes could be expanded to include drugs, environmental effects, etc.

In Step 8, the core query is intersected with the semantic classes to generate a filtered core query. For example, if ‘cataract\*’ is the unfiltered core query for retrieving the cataracts core literature, and if our semantic class of interest was ‘medicinal plants’, then the filtered core query would be (cataract\* AND “medicinal plants”). In Step 9, the filtered core query is inserted into the PubMed search engine, and the semantically filtered core records are retrieved.

In Step 10, the retrieved records (typically a few hundred) are read, and those that appear interesting (potential treatment for the medical problem being examined) are identified.

#### Development of the directly related literature query (cont’d)

Steps 11 and 12 constitute implementation of the second semantic filter. Text and MeSH patterns (mainly combinations) characteristic of the ‘interesting’ core records are identified, for future use in helping to formulate the directly related literature query. In parallel, Step 13 is conducted to analyze the interesting core literature concepts. For example, are there classes of concepts that will allow generalization beyond individual interesting concepts and might offer further insights into treatment mechanisms?

In Step 7, the outputs from Steps 5, 6, 11, and 12 are combined to generate the directly related literature query. This query will reflect the thrusts defined by the different grouping procedures, and may include combinations of terms that reflect the patterns in the ‘interesting’ core literature records. Thus, while numerical filters are not employed as in other ODS LRD techniques, two semantic filters are used to narrow the scope of the retrieval, and sharpen the focus on promising concepts.

#### 1.4.1.2 Frame 2

Development of the indirectly related literature query; identification of potential discovery candidates from the directly related literature

In Frame 2, Step 1 is generation of the directly related literature query, defined in Frame 1. Step 2 is insertion of this query into the PubMed search engine to retrieve the directly related literature records from Medline. Steps 3-6 are analogous to Steps 3-6 from Frame 1. Steps 8-9, application of the

first semantic filter, are analogous to Steps 8-9 from Frame 1. Step 10 is identification of potential discovery candidates from the filtered directly related literature. The common feature Step 10 in Frame 2 shares with Step 10 in Frame 1 is that both search for interesting records/concepts. In Frame 1, these interesting concepts are not potential discoveries, since they are in the core literature, whereas in Frame 2 they are potential discovery candidates, since they are not in the core literature.

Steps 11 and 12 in Frame 2 are analogous to their counterparts in Frame 1. The combination of Steps 5, 6, 11, and 12 in Frame 2 to generate the indirectly related literature query is analogous to the similar process to generate the directly related literature query from Frame 1. The remaining steps in Frame 2 have no counterpart in Frame 1.

Steps 1-12 resulted in a) generation of a query for retrieving the indirectly related literature and b) identification of potential discovery candidates based on the Medline database and use of MeSH-based semantic filters. Sub-sets of these steps were used for the Cataracts, PD, and MS medical studies. Steps 14-19 use a different type of semantic filter to identify potential discovery candidates, and these steps formed the basis of the RP medical study. In Step 18, the analyst inspects all the phrases visually, and selects those from desired classes. In Step 19, the analyst then examines the records in which those phrases occur, and identifies potential discovery candidates.

The main difference between the two processes is that Step 18 involves visual inspection of all phrases generated by the phrase frequency analyzer, while Step 8 uses MeSH filtering for selecting the semantic classes desired. Step 18 is obviously much more labor intensive than Step 8. The semantic filtering is performed by the analyst selecting phrases of the class desired for the solution. Thus, if the analyst is interested in non-drug approaches to addressing the medical problem of interest, the analyst will select only those phrases that represent non-drug approaches for further analysis.

The benefit of the approach represented by Steps 14-19 is the independence of the process from third-party indexers and omissions of indexing. In theory, all records that contain phrases from the desired semantic classes will be accessed. The deficiencies of this approach are that applicable records that do not contain the desired phrases in their Abstract will not be accessed (whereas MeSH-based records would in theory access these

records), and the labor intensity of the process. The combination of these two approaches, as depicted in Frame 2, would in theory eliminate the weaknesses of each approach and enhance the strengths. We did not combine the two approaches for any one study because of resource limitations.

### Identifying potential discovery candidates through citation relations

Steps 1-12 and 14-19 represent two approaches for identifying potential discovery candidates that were used in part by different studies reported in this monograph. Steps 13, 20, and 21 represent another approach for identifying potential discovery candidates. After potential discovery candidates have been identified from Steps 10 and/or 19, their records are located in the SCI. Then, citation linkages are used to identify other potential discovery candidates.

Specifically, approaches A, B, and C below were explored to identify additional potential discovery candidates, and approaches D, E, and F will be explored in future studies to identify additional discovery candidates.

- A. Documents in the References section of the relevant record
- B. Documents that cite the relevant record
- C. Documents that share one of more References with the relevant record
- D. Documents in the References section of the new relevant records identified in A, B, and/or C.
- E. Documents that cite the new relevant records identified in A, B, and/or C.
- F. Documents that share one or more References with the new relevant records identified in A, B, and/or C.

We had only begun to scratch the surface of this relational citation approach; it was employed only at the very end of the RP study and at the end of some of the other studies as well. It appeared to offer enormous potential for uncovering additional potential discovery candidates.

### Vetting potential discovery candidates

Irrespective of which of the above three processes were used to identify potential discovery candidates, the candidates had to be vetted before they could be considered as potential discoveries. Steps 22-25 constitute the vetting process that was used.

The purpose of our vetting procedures is to insure that what we report as potential discovery has not been found in the literature previously (i.e., no prior art), and obeys the criteria for discovery set forth at the beginning of the Introductory paper: **linking two or more literature concepts that have heretofore not been linked (i.e., disjoint), in order to produce novel, interesting, plausible, and intelligible knowledge.** If a concept has been found in the literature previously, but we believe its reporting would accelerate its development, we might report it as a potential innovation candidate. We have instituted a four step vetting process that balances thoroughness with pragmatism.

The first step (Step 22) is to check for appearance of the potential discovery concept in the core target problem research literature. How do we define this literature? There are two issues here: the database(s) selected as source material, and the technical scope of the problem. For database(s) selection, ideally, every research document published globally in the core problem area would constitute this core literature source(s). The practical compromise we have made is to define the core literature source(s) for the core target problem literature as the SCI and MEDLINE. While we believe this is a bare minimum core literature requirement to search for prior art/science, some examples overviewed in the Background section of the introductory paper and shown in more detail in [17,18] illustrate that even this threshold requirement was not met before potential discovery was claimed in the published literature. The technical scope is subjective, and flows from the original problem definition.

In this first vetting step, we check operationally for the intersection of the core target problem literature with the potential discovery literature. If the intersection is a null set, the first check is successful. Thus, if we check whether Fish Oil is a potential discovery for RP, we might use the query Fish Oil (or its many specific variants) and RP (or its variants), and see whether any records are retrieved. The real issue here is how broadly or narrowly we define the core target problem literature and the potential discovery concept literature. The breadth of definition could determine whether we have generated discovery, innovation, or nothing. For example,



Fish Oil may or may not be a discovery for treating RP, depending on whether we define the core RP literature to include or exclude the Peripheral Vascular Disease literature.

The second vetting step (Step 23) could be viewed as a continuation of the first step. We go beyond simple intersection to see whether there are citation linkages between the potential discovery concept and the core target problem literature that would indicate researchers were aware of the linking between these literatures previously. Citation linkages were only used for the SCI database, since this database is structured to exploit citation relationships. There are many types of citation linkages (citing papers, cited papers, papers that share common references, papers that share common citing papers, etc). Depending on how far we plan to proceed with a potential discovery (e.g., do we want to patent the potential discovery), we check at least the citing papers for linkages between the concept literature and the problem literature.

The third vetting step (Step 24) is checking the patent literature. This is more difficult than the first step because of the breadth and scope of the claims in each patent. We read the claims thoroughly to check whether a linkage has been established, or whether the inventor has generated unsubstantiated claims. Most of the prior art exclusion of potential discovery candidates by the vetting process has occurred in this patent step.

Why does this exclusion occur mainly in the patent step, and how can it be overcome? In the ODS LBD medical studies reported in this monograph, and in essentially all the ODS LBD medical studies reported in the literature, the potential discovery algorithms are focused on Medline. This allows exploitation of the MeSH taxonomy capabilities. We exclude the medical problem core literature in Medline as part of the algorithm, which (except for some of the MeSH anomalies noted previously) essentially eliminates the vetting problem in Medline. Since there is much overlap between the laboratory research in Medline and SCI records, most (not all) prior art in the SCI will also be eliminated by the exclusion portion of the potential discovery algorithms.

The patent literature is very different from the SCI and Medline. Many of the authors are different; many people patent rather than publish, among other differences. Therefore, core literature concepts that were excluded from Medline (and effectively SCI) by the algorithms could (and do) occur

in the patent literature. The obvious method for insuring that core literature concepts are excluded from the patent literature (and SCI) is to apply the potential discovery algorithms, with their core literature exclusion component, to the patent literature and SCI as well as to Medline. This approach would complicate the analytical procedure, since the SCI and patent literature do not have the MeSH capability, and the simplifications offered by the MeSH capability could not be exploited. For the proof-of-principle demonstrations reported in this monograph, we have chosen to exploit the MeSH capabilities and devote the extra effort required to vet the patent and SCI literatures.

All vetting steps are run serially. Once the first three vetting steps have been taken successfully, we then have the potential discovery candidate concepts examined by technical experts (Step 25). We access two types of technical experts: those expert in the core target problem literature (e.g., RP), and those expert in the potential discovery concept literature (e.g., Fish Oil). We ask the experts in the core target problem literature whether the potential discovery concept is indeed discovery (i.e., have they seen it before in the target problem context), and we ask the experts in the potential discovery concept literatures whether the concept could be extrapolated to the target problem. If we report potential discovery concepts that have been vetted partially, we state that fact.

How do our vetting procedures compare with those used by the remainder of the ODS LBD research community? We see little discussion of vetting in the open ODS LBD literature, and therefore it is difficult to compare our vetting approaches with others on the basis of published protocols. We applied the first and third vetting steps above to a number of potential ‘discoveries’ claimed in the mainstream literature, using only the terminology supplied by the authors and only the major databases, and have found that many of these potential ‘discoveries’ would have been excluded by our process [17-19].

Had we performed steps 1 and 2 only (Medline and the SCI) for our vetting procedure, we would have had substantially more potential ‘discoveries’. However, we believe that presenting such results as potential ‘discoveries’ to independent third parties would have impacted the credibility of our findings adversely, and would have cast doubt on the credibility of our whole approach. Therefore, we wanted to define discovery in the sense in which it

is understood by most of the technical community, and designed our vetting process to support that goal.

As shown on Frame 2, for Steps 22-24, there are two decision points. If a potential discovery candidate fails at any of these three steps, it is added to the ‘interesting’ concepts in the core literature (Step 26) defined in Frame 1 (shown in Step 13). If a potential discovery candidate passes all four decision points, it is then added to the pool of potential discovery (Step 27), and is subjected to further analysis (Step 28).

#### 1.4.1.3 Frame 3

Identification of potential discovery candidates from the indirectly related literature

The steps in Frame 3 are analogous to those in Frame 2, with the exception that the steps necessary for defining a query (Steps 3, 4, 5, 6, 7, 11, and 12 in Frame 2) are eliminated in Frame 3, since we have terminated the process at the query for retrieving the indirectly related literature. Obviously, there are different levels of indirectly related literatures, and the frames could have been continued ad infinitum to identify literatures further and further removed from the core. Terminating the process at the first indirect literature represents a compromise between marginal recall and marginal effort.

### 1.4.2 Description of Specific Medical Studies Approaches

#### 1.4.2.1 Raynaud’s Phenomenon

The RP study [20] was the first medical ODS LBD study we performed. For the RP study, we used Steps 1, 2, 14, 15, 16, 18 in sequence from Frame 1, Steps 1, 2, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 in sequence from Frame 2, and Steps 1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 15, 16, 17, 18, and 19 in sequence from Frame 3. Basically, we did not take advantage of the semantic class restrictions offered by use of the MeSH terms.

#### 1.4.2.2 Cataracts

The Cataracts study [21] was the second medical ODS LBD study we performed. The main objective was to reduce the time required for the RP

study, while still generating copious amounts of potential discovery. For this study, we used Steps 1-6, 8-13 and 7 in sequence from Frame 1, Steps 1-6, 8-12, 13, 20-28 from Frame 2, and Steps 1, 7-19 from Frame 3. We took advantage of MeSH terms as semantic filters (Filters A and B on the different Frames) to streamline the total process.

#### 1.4.2.3 Parkinson's Disease

The PD study [22] was the third medical ODS LBD study we performed. The objective was to build upon our experience with the Cataracts study, and make more extensive use of the semantic filter 'B' terms. For this study, we used Steps 1-6, 8-13 and 7 in sequence from Frame 1, Steps 1-6, 8-12, 13, 20-28 from Frame 2, and Steps 1, 7-19 from Frame 3.

#### 1.4.2.4 Multiple Sclerosis

The MS study [23] was the fourth medical ODS LBD study we performed. The objective was to build upon our experience with the Cataracts and PD studies, and use more of the features in the expanded flow chart depicted by Figure 2. For this study, we used Steps 1-6, 8-13 and 7 in sequence from Frame 1, Steps 1-6, 8-12, 13, 20-28 from Frame 2, and Steps 1, 7-19 from Frame 3.

### 1.4.3 Description of Non-Medical Studies Approach

#### 1.4.3.1 Overall

For the WP non-medical study [24], two separate techniques were used, and they each differed somewhat from the specific technique used for the medical studies. The two MeSH-based filters shown in Figure 2 could not be used in the non-medical studies because of the lack of an available taxonomy for the non-medical studies.

Overall, a core literature query (consisting of hundreds of terms) was defined for WP using an iterative relevance feedback technique [8]. Then, an expanded (related) literature was defined through clustering of the core literature, and selecting/generalizing key phrases from each cluster. The expanded literature was searched by two different approaches for potential discovery candidates: Cluster Semantic Filtering (CSF) and Latent Semantic Indexing (LSI).

#### 1.4.3.2 Cluster Semantic Filtering

Cluster Semantic Filtering was somewhat analogous to the semantic filtering approach used in the RP study. In the RP study, semantic filtering was performed on phrases from the expanded literature to identify topics of interest, whereas in the WP study, semantic filtering was performed on document clusters in the expanded literature. Specifically, the expanded WP literature was stratified using large numbers of document clusters. Each cluster was inspected visually, and those clusters that appeared to focus on desired semantic classes and novel topics were selected for more detailed analyses. All documents contained within these ‘interesting’ clusters were evaluated for potential discovery, and the promising candidates were subjected to the further analyses depicted on Figure 2 (SCI linkages and vetting). It was found that the clustering served as a strong filter not only for segregating the semantic classes, but for separating the promising discovery candidates from those much less promising. CSF had some of the manual intensity characteristic of the RP process, but was somewhat less labor intensive.

For example, one of the problems in WP is fouling of the separation membranes. This results in greater maintenance time and costs, and eventually in higher WP costs. It would be desirable to reduce membrane fouling.

We examined an expanded and clustered anti-fouling literature. One interesting cluster focused on anti-fouling properties of sponges. Since this theme seemed very disparate from the core literature, interesting, and promising, we examined it in more detail. We found there were sponges that had intrinsic anti-fouling defenses, using some combination of chemical and biological mechanisms. Potential discovery could involve extracting anti-fouling substances excreted by or intrinsic to the sponges and perhaps applying them to WP separation membranes, or studying the anti-fouling mechanisms used by the sponges and creating similar mechanisms artificially.

#### 1.4.3.3 Latent Semantic Indexing

Operationally, we used a core article query to tag the core articles, and then tagged the remainder as expansion. We then clustered the core articles into

thematic groups, and used terminology from these groups as ‘seeds’ for linking to related terms from the expanded literature. Following Gordon and Dumais [12], we then computed the ranking metrics (cosine similarity) score between the selected core terms and the expanded terms in the projected LSI space. After sorting the expanded core terms based on their cosine similarity to the selected core term, we obtained a number of interesting associations. High ranking terms were examined, and much potential discovery surfaced (including potential discovery from single frequency concepts). See Figure 3 for a schematic of the LSI-based methodology.

FRAME 3

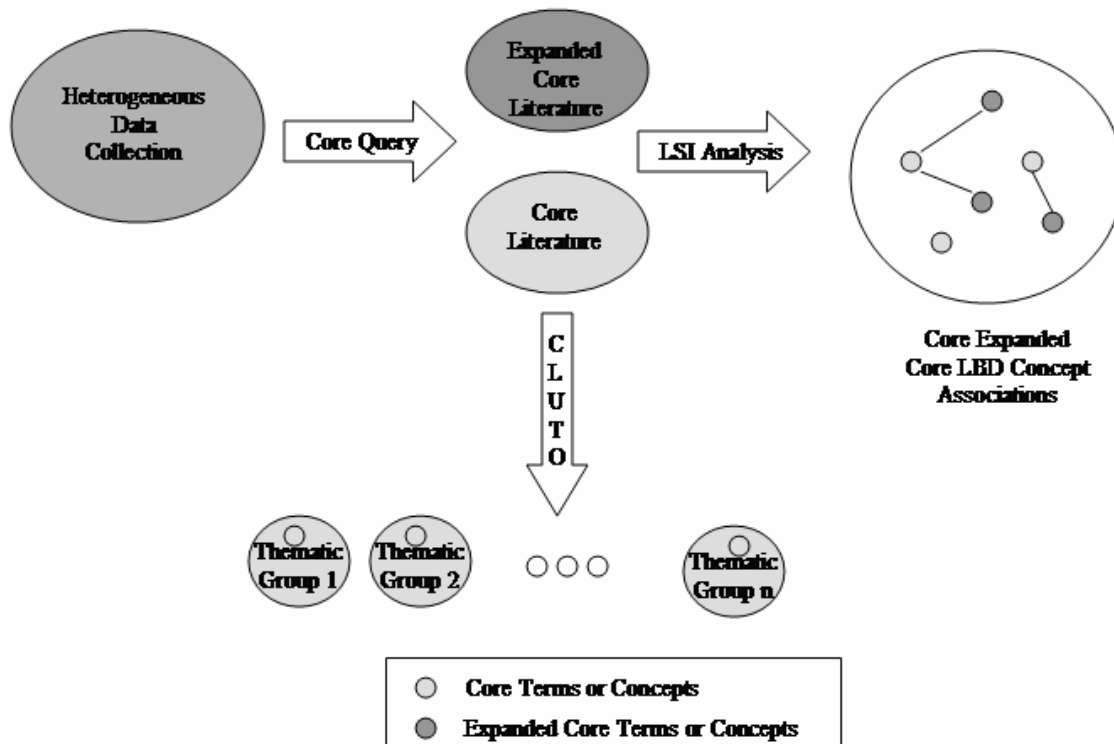


FIGURE 3 – LSI LBD METHODOLOGY

## **1.5 Specific Approaches and Results**

Now that the generic ODS LRD approach has been outlined, specific details of the approach for each variant used for discovery will be described, along with the results. Chronologically, the first problem addressed was the benchmark RP problem using ODS LBD, and it will be described in the next chapter in this monograph (also see [20]). A 2005 paper [10] outlined the clustering approach that was used to identify the main medical themes in the core literature.

The second medical problem addressed with ODS LBD was cataracts. A medical problem was selected as the second problem for two reasons: to show that the large number of potential discoveries from the first medical study (RP) were not a fluke, and to show that a ‘streamlined’ approach to radical discovery was possible with little loss in performance. The results of the cataracts study are reported in Chapter 4 (also see [21]).

A third medical problem, PD, was addressed through ODS LBD to gather further confirmatory data for the radical discovery approach. The semantic filters were applied more extensively in the PD study than in the cataracts study, and longer queries were used as well. The results of the PD study are reported in Chapter 5 (also see [22]).

A fourth medical problem, MS, was addressed with ODS LBD to further advance the technique, to improve the process steps depicted in the flow chart, and to ‘push the envelope’ on the bounds of the biomedical

phenomena component of the query. The results of the MS study are reported in Chapter 6 (also see [23]).

Also, for the first time, a non-medical application (WP) was studied with the use of both ODS LBD and ODS LAD. The purpose was to show that ODS LBD and ODS LAD need not be limited to medical problems, and that much potential discovery was possible with non-medical topics as well. The results of the WP study are reported in Chapter 7 (also see [24]).

It should be emphasized that in all five topics studied, the results obtained (while substantial) are the tip of the iceberg of what is possible with adequately resourced studies. The reasons behind this statement will be included in the following chapters.

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## **Chapter 3 - LITERATURE-RELATED DISCOVERY: POTENTIAL TREATMENTS FOR RAYNAUD'S PHENOMENON**

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### **1.1. Purpose and Overview of Study**

The goal of the present study is to re-visit the data used for Swanson's initial ODS LRD study on RP [1], and show that much more discovery is possible than identified by Swanson (or any of his successors who used the same data to validate their own ODS LRD approaches). In order to appreciate the results of the present study, some understanding of RP is required. An overview of RP will be presented before discussing the specific steps and results. Because the main RP terminology used in the literature is not consistent (in many cases, Raynaud's Disease is used interchangeably with Raynaud's Phenomenon or Raynaud's Syndrome), the overview will include the distinction among these Raynaud variants.

Following the RP overview, the specific methodology and results for the study are presented. After sample results are shown, potential improvements for an adequately resourced study are presented in detail.

### **1.2. Raynaud's Phenomenon Background**

RP is a condition in which small arteries and arterioles, most commonly in the fingers and toes, go into spasm (contract) and cause the skin to turn pale (blanching) or a patchy red (rubor) to blue (cyanosis). [2-4]. While this sequence is normally precipitated by exposure to cold, and subsequent re-warming, it can also be induced by anxiety or stress. Blanching represents the ischemic (lack of adequate blood flow) phase, caused by digital artery vasospasm. Cyanosis results from de-oxygenated blood in capillaries and venules (small veins). Upon re-warming, a hyperemic phase ensues, causing the digits to appear red. [5].

RP can be a primary or secondary disorder. When the signs of RP appear alone without any apparent underlying medical condition, it is called Primary Raynaud's, or formerly, Raynaud's Disease. In this condition, the blood vessels return to normal after each episode. Conversely, when RP occurs in association with an underlying condition or is due to an

identifiable cause, then it is referred to as Secondary Raynaud's, or formerly, as Raynaud's Syndrome. The most common underlying disorders associated with Secondary Raynaud's are the auto-immune disorders, or conditions in which a person produces antibodies against his or her own tissues [5]. In contrast to Primary Raynaud's, where the blood vessels remain anatomically normal after each episode, in Secondary Raynaud's there may be scarring and long-term damage to the blood vessels; thus, Secondary Raynaud's is potentially a more serious disorder than Primary. Certain repetitive activities may result in a predisposition to RP. These cases of so-called "Occupational Raynaud's" typically result from the chronic use of vibrating hand tools.

Thus, while RP is a direct consequence of reduced blood flow due to reversible blood vessel constriction, it may be a function of many variables that can impact blood flow. These include:

- \*Inflammation from the auto-immune disorders that can cause swelling and thereby constrict blood vessels;
- \*Increased sympathetic nervous system activity, which can affect the timing and duration of the blood vessel muscular contractions that cause constriction [6].
- \*Heightened digital vascular reactivity to vaso-constrictive stimuli, that cause the blood vessels to over-react and over-contract [6];
- \*Enhanced muscular tone of resistance arteries can reduce blood flow [7];
- \*Deposits along the blood vessel walls that can reduce blood flow and increase the flow sensitivity to contraction stimuli;
- \*Blood rheological properties that offer additional resistance to blood flow, and magnify the impact of blood vessel constriction;
- \*Blood constituents and hormones that can act as vaso-constrictors or vaso-dilators.

### **1.3. Specific Approach – Raynaud's Phenomenon**

The specific ODS LRD process used will now be described. Chapter 2 outlined the ODS LRD process steps in its Figures 1 and 2 (also see [8]). Figure 1 divided the ODS LRD process into front-end and back-end components generically. The present section describes the front-end and back-end components specifically. First, the core literature retrieval will be described. Then, the expansion of the core literature to directly and indirectly related literatures will be discussed, completing the description of

the front-end component. Third, identification of potential discovery candidates will be shown, followed by selection of hypothesized discovery items.

### **1.3.1. Core Literature Retrieval**

The most critical step in the total process is generating a comprehensive core literature. The core literature is the starting point for the literature expansion process, and any gaps in the core literature will translate into gaps in the expanded literature.

MEDLINE was the database selected as the main source medical literature, for two reasons. First, it is regarded widely as the premier medical literature. Second, it was the prime literature used in Swanson's initial ODS LRD study, and one objective of the present study was to use the same data source as Swanson's benchmark study. PubMed was used to search the MEDLINE database. Near the end of the study, the SCI [9] was used to identify additional potential discovery through citation linkages.

'Raynaud's Disease' is a MESH term (MESH is a controlled vocabulary in MEDLINE assigned to each record), and use of the MESH term as a query term retrieved most of the final records used. As a result of some query iterations, Raynaud\* was added to the text word field search to arrive at the final query used: (Raynaud's Disease OR Raynaud\* [TiAb]). This query would retrieve all records that had 'Raynaud's Disease' as a MESH term, or had Raynaud\* in the Title or Abstract.

### **1.3.2. Core Literature Expansion**

The next most critical step in the total process is generating a comprehensive expanded literature related directly and indirectly to the core literature. This expanded literature serves as the source of potential discovery. There are many ways to expand the core literature, and they all involve a tradeoff between comprehensive coverage and availability of resources.

Probably the most comprehensive approach would be that described in the query expansion examples of [10]. A phrase frequency analysis would be performed on the core literature. Each phrase would then be generalized to access myriad literatures related to the core literature component from which it originated.

For example, suppose a phrase from the core RP literature is ‘blood viscosity’. The first level of expansion is to retrieve all records from MEDLINE either directly containing the phrase ‘blood viscosity’ or subsumed under the MESH term ‘blood viscosity’, then subtract out the records contained in the core RP literature. This would leave blood viscosity-related records that were not in the core RP literature. The second level of expansion is to retrieve all records from MEDLINE containing synonyms of ‘blood viscosity’, such as ‘blood rheology’, and again subtract RP core records from the retrieval. The third level of expansion is to generalize ‘blood viscosity’ (to ‘viscosity’, for example), retrieve all records from MEDLINE containing ‘viscosity’, then subtract MEDLINE core records from the retrieval as well as all MEDLINE ‘blood viscosity’ records if the first level of expansion was used, as described above.

However, there are tens of thousands of phrases that can be extracted from the core RP literature, and applying the above levels of expansion to each phrase becomes an overwhelming process. While there are multiple ways to simplify this process, the following simplification steps were used in the RP study and in other on-going studies as well.

The documents in the RP core literature were clustered into the main thematic groups. A number of clustering approaches were tested (manual clustering, multi-link word/ phrase clustering, factor matrix clustering, and document clustering). They all produced the same major themes.

Then, words and phrases that represented each major theme and were judged to be significant were selected for the expansion process described above. An iterative approach was used [11] to arrive at the final query.

### **1.3.3. Identification of Potential Discovery Candidates**

As will be seen in the results section of this chapter, almost two orders of magnitude more potential discovery were generated by the present approach than all other reported ODS LRD approaches on the RP treatment problem. While the comprehensiveness of the core literature expansion process played some role in this result, the authors believe that the discovery candidate identification approach of the present section deserves much of the credit. How does this approach differ from previous discovery candidate approaches, and why does it result in the high levels of discovery?

To answer that question, it is necessary to discuss the discovery candidate selection problem in general, and the previous discovery candidate selection approaches in particular. The starting point is the expanded literature.

In our limited expansion process for the RP study, after the core literature had been removed from the total literature retrieved, tens of thousands of records remained (a broader expansion could have yielded on the order of ~100000 records or more). Phrase frequency analysis of this remaining literature (identifying all the different phrases in these records and their frequencies of occurrence) yielded hundreds of thousands of words and phrases. To make the problem more tractable, it would have been highly desirable to rank the phrases by discovery potential, or at least filter out the least likely discovery candidates.

As we showed in the Background section of Chapter 1 (also see [12]), when discussing Swanson's concept, there appear to be no unique numerical conditions associated with discovery. Application of arbitrary numerical filters probably eliminated most of the potential discovery in past studies.

We removed the two conditions discussed in [10] as candidate discovery filter/ ranking metrics for the expanded literature. The only filter employed required that candidate discovery items be in the class of food, food derivative, food-related substance, or lifestyle factor, and not be drugs or drug-related. Swanson discussed use of a similar strategy for a study on migraine ("Each set of records formed by searching titles for each B-word is to be narrowed down to certain categories of records (chosen in advance) that are likely to contain target words of particular interest..... In the present migraine example, the strategy was designed to restrict the output to dietary factors or deficiencies induced by dietary deprivation.") [13].

Now we proceed to describe our ODS LRD approach for the RP problem. We clustered the RP core literature into its main Circulation and Auto-immunity categories [14,15], then focused on addressing the peripheral circulation sub-component. Focusing on the peripheral circulation component is in line with what past ODS LRD studies on this topic have done, although our using proper clustering to arrive at the major thrust areas is the first systematic approach we have seen reported. There were three major medical themes that characterized this RP peripheral circulation sub-component (blood viscosity, platelet aggregation, vasoconstriction). If

literatures for each of these three thematic areas were retrieved from the source database, and the intersection of the RP core literature with the three retrieved literatures removed, then the remaining non-RP portions of these three retrieved literatures could be viewed as related directly to the core RP literature.

Therefore, it was decided to access and examine a few indirectly related literatures. Only one of the three directly related literatures (Blood Viscosity) was used as a base for generating indirectly related literatures. The choice of literatures for further expansion was dictated by the extremely limited resources available. The smallest by far of the three directly related literatures, Blood Viscosity, was expanded vertically and horizontally into three indirectly related literatures.

The vertical expansion involved clustering the blood viscosity literature, and then retrieving literatures based on the terminology of each component cluster. There were two main component literatures of blood viscosity: fibrinogen and cell deformability. These literatures were retrieved from PubMed, and again the core literature and directly related literatures were subtracted from the retrieval.

The horizontal expansion involved generalizing the blood viscosity literature into all viscosity (blood and non-blood), then subtracting out the blood viscosity literature to obtain its complement, the non-blood viscosity literature (e.g., saliva viscosity, synovial fluid viscosity, etc). This literature was retrieved from PubMed, and again the core literature was subtracted from the retrieval.

In total, there were six related literatures that would serve as sources for potential discovery: three were related directly to the core RP literature, and three related indirectly. All the phrases in each of the six literatures (~270000 phrases with frequency two or greater) were inspected visually, and those that met the criteria of the previous section (members of specific pre-selected categories like food, food derivatives, etc) were identified as potential discovery candidates.

Then, each of the candidate discovery phrases was used as a query term to retrieve articles from the appropriate sub-set of the six thematic literatures. Thus, if the phrase 'Fish Oil' occurred in four of the six expansion literatures, then 'Fish Oil' was used as a query term to retrieve articles



containing ‘Fish Oil’ in each of these four literatures. The articles were read, and evaluated for relevance with the use of two metrics: 1) Importance of the article to addressing the RP problem, and 2) Strength of the discovery (essentially, does it not appear in the RP literature prior to 1986, and is it relatively unique). Three bands (LO, MED, HI) were used to quantify each metric.

We also demonstrated use of citations for identifying additional potential discovery concepts as described in Chapter 2 (also see [8]). We had only begun to scratch the surface of this relational citation approach; it was employed at the very end of the RP study. It appeared to offer enormous potential for uncovering additional potential discovery candidates.

## **1.4. Results – Raynaud’s Phenomenon**

### **1.4.1. Core Literature Retrieval**

The final core literature query (Raynaud’s Disease [MH} OR Raynaud\* [TiAb]) was inserted into PubMed for the period 1975-1985, and 1610 records were retrieved, of which 930 were listed by MEDLINE as having had Abstracts.

### **1.4.2. Core Literature Taxonomies for Major RP Theme Identification**

The 930 articles with Abstracts were clustered using a variety of approaches [14,15]. All the taxonomies had two first level categories: Auto-Immunity and Circulation. Auto-Immunity can be viewed as a characteristic of Secondary Raynaud’s, while Circulation can be viewed as symptoms resulting from Primary and Secondary Raynaud’s. It was decided to focus on Circulation only for the initial demonstration of the technique, since this was the focus of Swanson’s paper. Further, the second level of the various taxonomies showed that Circulation could be divided into Peripheral Circulation and Coronary Circulation. Lower levels of the taxonomies showed that Peripheral Circulation could be divided into three major themes: blood viscosity, platelet aggregation, and vasoconstriction. These were the main themes explored for discovery in the present chapter.

### **1.4.3. Core Literature Expansion**

Using the iterative query development techniques of Simulated Nucleation [11], queries were developed for each of the three themes above. The three queries are as follows:

#### Blood Viscosity

"BLOOD VISCOSITY" OR "ERYTHROCYTE DEFORMABILITY" OR "RED CELL DEFORMABILITY" OR "PLASMA VISCOSITY" OR "PLASMA FIBRINOGEN" OR HYPERVISCOSITY OR ("SHEAR RATE\*" AND ("RED CELL\*" OR ERYTHROCYTE\* OR BLOOD))

#### Platelet Aggregation

"PLATELET ACTIVATION" OR "PLATELET AGGREGATION" OR "PLATELET FUNCTION" OR "ENDOTHELIAL DAMAGE" OR "ENDOTHELIAL SWELLING"

#### Vasoconstriction

VASODILAT\* OR "VASCULAR REACTIVITY" OR "PERIPHERAL VASCULAR RESISTANCE" OR "VASOSPAS\*" OR "VASOCONSTRICT\*"

These queries were inserted into PubMed, and three literatures were retrieved. The Blood Viscosity literature contained 3493 records; the Platelet Aggregation literature contained 11647 records; the Vasoconstriction literature contained 11031 records. The RP core literature records were subtracted from each of the three literatures to produce three expanded literatures.

These three literatures could be viewed as related directly to the core literature. As stated previously, three indirectly related literatures were also generated. The queries for the three indirectly related literatures are as follows:

#### Deformability

"CELL DEFORMABILITY" OR "CELL FILTRATION" OR "CELL FILTERABILITY"

#### Fibrinogen

FIBRINOGEN

#### Non-Blood Viscosity

VISCOSITY NOT ("BLOOD VISCOSITY" OR "ERYTHROCYTE DEFORMABILITY" OR "RED CELL DEFORMABILITY" OR "PLASMA VISCOSITY" OR "PLASMA FIBRINOGEN" OR HYPERVISCOSITY OR ("SHEAR RATE\*" AND ("RED CELL\*" OR ERYTHROCYTE\* OR BLOOD))))

These latter queries were inserted into the PubMed search engine [16], and 303 records were returned for the Deformability literature, 8555 records were returned for the Fibrinogen literature, and 4142 records were returned for the Non-Blood Viscosity literature. In total, there were 39171 records in these six related literatures.

#### **1.4.4. Identification of Potential Discovery Candidates**

Phrase frequency analyses were performed on Abstracts of these six essentially orthogonal literatures, and 271016 phrases with occurrence frequency of two or greater were generated.

These 271016 phrases constituted all the single, adjacent double, and adjacent triple word phrases in the combined six literatures with a frequency of two or greater, and were the phrases used to search for discovery. There were 1146043 phrases total when singly occurring phrases were included (72824 single word phrases, 300874 adjacent double word phrases, and 682345 adjacent triple word phrases). **Resource limitations prevented the analysis of singly occurring phrases.**

The 271016 phrases were inspected visually, and 1482 phrase-literature combinations were identified initially as potential discovery candidates. A phrase-literature combination is defined as the occurrence of a phrase in one of the six expanded literatures. Thus, if the phrase 'Fish Oil' occurred in four of the six expanded literatures, and 'Fish Oil' was judged to be in the appropriate potential discovery category (food, food derivative), then four phrase-literature combinations had to be examined for potential discovery. The 1482 phrase-literature combinations were examined in some detail, very similar phrases were combined, non-relevant phrases were eliminated, and 650 phrase-literature combinations remained to be investigated in detail.

#### **1.4.5. Selection of Potential Discovery Candidates**

The 650 phrase-literature combinations were divided among some of the participants, and all the records in each phrase-literature combination were evaluated. Thus, if ten records in the blood viscosity expanded literature contained the phrase ‘Fish Oil’, then each of the ten records’ Abstracts was read, and a judgment was made as to the level of discovery contained in each record (if any). The two metrics were evaluated for each record retrieved. Each evaluated record that was judged to contain some degree of potential discovery is listed in Appendix 1 of this monograph.

#### **1.4.6. Vetting of Potential RP Discovery Candidates**

In the RP study, we used a more stringent time frame criterion than the other reported ODS LRD studies. Initially, we checked the RP core literature for the concept’s appearance for the time frame 1975-mid-1985, the time frame that Swanson reported in his initial RP paper [1]. Then we reasoned that if our concept were to be a true discovery, it could not have appeared in the RP core literature before then. We then checked the titles and MESH terms in the RP core literature prior to 1975 (Abstracts were not available in that period), and eliminated some very promising potential discoveries that had not appeared in the 1975-1985 time frame check (e.g., phenyl-3-dibutylaminoethylamino-5 oxadiazole, Micoren, Piperazine, Tryptophan, Vasopressin, Ginkgo Biloba, Kallikrein). Some of these may have fallen through the cracks and may not have been referenced for decades, and could very well be classified as potential innovations.

#### **1.4.7. Potential Discoveries for Raynaud’s Phenomenon**

Table 1 contains a handful of the ~130 potential RP treatment discoveries found so far. These ~130 potential discoveries represent the tip of the iceberg, for the following reasons:

- Only a small fraction of the possible expanded literatures was used
- Mainly non-biomedical personnel were involved in the discovery identification process, and were not equipped to identify the more subtle relationships
- The ~900000 phrases with a frequency of unity were not examined for potential discovery. From the rare event perspective discussed above, and in Chapter 1, these rare phrases may have had the most potential for discovery! Coupled with a more complete expanded literature, the

unity frequency phrases could total well over a million, and serve as a veritable ‘gold mine’ for discovery

- The citation-based discovery pathways had only been used for a minute number of cases, and these pathways offered enormous potential for discovery

In Table 1, the first column contains the potential discovery, the second column contains the two part evaluation metric applied to vasoconstriction (the first part of the metric addresses the importance of the concept to addressing the vasoconstriction problem, and the second part addresses the strength of the discovery [essentially, does it appear in the RP literature prior to 1986, and is it relatively unique]), the third column contains the two part evaluation metric applied to platelet aggregation, the fourth column contains the two part evaluation metric applied to blood viscosity, and the fifth column uses literature quotes to summarize why we believe the substance will impact the specific medical problem in the previous three columns.

**TABLE 1 – POTENTIAL DISCOVERY CANDIDATES FOR TREATING RAYNAUD’S PHENOMENON (FULLY VETTED)**

| DISCOVERY  | VAS      | AGG      | VIS     | EFFECT   |
|--|----------|----------|---------|--|
| Fish Oil/ Salmon/ Menhaden/ Cod Liver Oil/ Eicosapentaenoic Acid (EPA)/ Docosahexaenoic Acid (DHA) | MED/ MED | HI/ MED  | HI/ MED | Augmentation of contractile effect of norepinephrine .... diminished by dietary intake of EPA (Lockette et al, 1982); DHA .... inhibited aggregation of platelets .... Shift of the prostaglandin I/thromboxane A balance to a more antiaggregatory and vasodilatory state [17]  |
| Agar-Agar  | HI/ MED  |          |         | The increased diameter (+ 35.78%) confirms the peripheral vasodilating theophylline effect [18]  |
| Enkephalins  | HI/ MED  |          |         | Intraarterially administered enkephalins exert a vasodilatory effect on vasculature in skeletal muscle which may be direct, indirect or both. [19]   |
| Nitric Oxide   | MED/ MED | MED/ MED |         | Vascular smooth muscle relaxation elicited by nitrogen oxide-containing vasodilators. Nitrovasodilators are thought to form nitric oxide free radical and directly activate guanylate cyclase. ... S-nitrosothiols could serve as active intermediates in the inhibitory action of sodium nitroprusside, nitric oxide, and related nitrogen oxides on platelet aggregation [20-22] |
| Benzoic Acid   | HI/ MED  | MED/ MED | HI/ HI  | PG analog .... [(+)-4-(3-[3-[2-(1-hydroxycyclohexyl)-ethyl]-4-oxo-thiazolidinyl]-propyl) benzoic acid] ... is a potent arterial vasodilator. .... 2,3-Dihydroxybenzoic acid (2,3-DHB) inhibits the second wave of platelet aggregation .... The effect of hexobendine ... on the dynamic viscosity of blood-isotonic and   |

|  |             |           |             |  |
|--|-------------|-----------|-------------|--|
|  |             |           |             | hyperosmolal suspensions of human and rat erythrocytes .... caused a statistically significant reduction of viscosity [23-26]  |
| Reflexotherapy (RT)  | MED/<br>MED |           |             | After RT was completed ..... the total peripheral vascular resistance dropped both at rest and after exercise. [27]  |
| Huang Chin extract (Scutellaria baicalensis George)        | MED/<br>MED |           |             | Huang Chin extract produces peripheral vasodilatation which leads to a hypothermia in conscious rats. The hypothermia in response to Huang Chin application was brought about solely by cutaneous vasodilatation [28]  |
| Secretin   | MED/<br>MED |           |             | Secretin produced similar vasodilation in all organs .... duodenum, jejunum, heart, kidney, forelimb, spleen, and the skin and muscle of the forelimb [29-31]  |
| Vernolepin/ Dried Fruit                                    |             | HI/<br>HI |             | The first pharmacological characterization of vernolepin revealed ... an antiaggregating and disaggregating activity against rabbit platelet aggregation induced by arachidonic acid [32]  |
| Guar Gum   |             |           | MED/<br>MED | .... guar gum for 4 weeks. They experienced a decrease in (1) plasma fibrinogen, (2) insulin requirement, (3) serum osmolality and (4) plasma viscosity; and an increase in serum albumin and total serum protein concentrations. The decrease in plasma viscosity, which was statistically significant [33] |
| Cell Hydration/<br>Hydration/Dehydration/<br>Hypohydration |             |           | HI/<br>HI   | Optimal rheologic behavior was exhibited by normal RBC when their water content was in the normal range. A rise or a fall in cell hydration resulted in a decrease in cell deformability ..... Maximal arm blood flow was reduced by nearly 50% in hypohydration. [34,35]                                    |

By far, the highest frequency concept was fish oil and its constituents, and there were many articles on the different expressions of fish/ fish oil (e.g., fish oil, marine oil, herring oil, sardine oil, mixed fish, seafood, mackerel, menhaden, cod liver oil, etc). Very few of these articles are displayed in the table above.

In the Background section of Chapter 1, we address the original Swanson RP study, and conclude that the fish oil finding was marginal discovery at best, and could have as easily been classified as an innovation. We include it here for purposes of completeness.

While the fish-related records tended to be high frequency, most of the remaining concepts records were low (typically very low) frequency. This corresponds to the philosophy espoused previously, namely, that the chances of high frequency concepts resulting in true discovery are low.

Most of the potential discoveries impact vasoconstriction or platelet aggregation. Relatively few impact blood viscosity. This is partly due to the fact that the bulk of the literatures examined were focused on vasoconstriction or platelet aggregation.

## 1.5 Conclusions

The picture from Table 1 and the remainder of the ~130 potential discoveries (and the hundreds of additional discoveries possible with a properly resourced study) is a synergy of lifestyle/dietary practices that could be interpreted as ***circulation-enhancing***. Along with non-discovery items such as no smoking, no butter, no margarine or trans fats, no carrageenan, less coffee, less sucrose, and more endurance exercise are discovery-based admonitions to eat more fish/ fish oils, onion, garlic, ginger, natto, artichoke, pineapple, melon, mushrooms, mussels, peanuts, water, have periodic fasting, include some of the herbs/ plants mentioned in the list, include supplements such as Coenzyme Q10, Selenium, Germanium, and Melatonin, and include stress-reduction measures such as reflexotherapy and adequate bed rest. As stated above, more laboratory tests and field trials would have to be done on all these items to insure that they are circulation-enhancing and safe, but these preliminary literature-based results offer some promise of what is possible. Further, these are potential discoveries based on data over two decades old. For serious treatments, the study should be re-done with adequate resources, the latest data, and the knowledge expressed as the lessons learned from the present study.

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## **Chapter 4 - LITERATURE-RELATED DISCOVERY: POTENTIAL TREATMENTS FOR CATARACTS**

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### **1.1. Overview of Study**

Chapter 4 presents a comprehensive approach for systematic acceleration of discovery, and demonstrates the generation of large amounts of potential discovery for prevention/treatment of cataracts. This chapter is the second of our medical studies, and follows the manually intensive study of RP in Chapter 3 (also see [1]). The definitions of discovery and innovation and the approach background were shown in Chapter 1 (also see [2]), and the approach methodology was shown in Chapter 2 (also see [3]). The present chapter provides an overview of the etiology and treatment of cataracts, then proceeds to retrieve and analyze the core cataracts literature, and literatures related directly and indirectly to the core cataracts literature. These related literatures contain the seeds of potential discovery for cataracts treatment and understanding, and some examples of potential discovery are presented for both classes of related literatures. Also, examples of interesting but non-discovery concepts from the core cataracts literature are presented, since they have practical value in their own right.

### **1.2. Purpose of Study**

We selected the subject of cataracts because of its global prevalence, and its apparent intractability to all treatments except for surgery. Our first goal was to identify non-drug non-surgical treatments that could potentially 1) prevent cataracts, or 2) reduce the progression rate of cataracts, or 3) stop the progression of cataracts, or 4) maybe even reverse the progression of cataracts. Our second goal was to demonstrate that we could solve an ODS LRD problem with no prior knowledge of any results or prior work (unlike the case with the RP problem).

Our third goal was to determine whether large time savings in the discovery process were possible relative to the time required for conducting the RP study. To that end, we used the MeSH taxonomy of MEDLINE to restrict potential discoveries to selected semantic classes. As will be shown, we generated large amounts of potential discovery in more than an order of magnitude less time than required for the RP study.

### 1.3. Cataracts Background

A cataract is a clouding or opaque area over the normally transparent lens of the eye, caused when some of the protein that makes up the lens begins to clump together and interferes with vision. As this thickening occurs, it prevents light rays from passing through the lens and focusing on the retina. [4].

Suspected causes of cataracts include smoking, diabetes, excessive exposure to sunlight, high altitudes, steroid use, diuretic use, and certain major tranquilizers. [5]. For several of the latter potential causes listed (i.e., steroids, diuretics, and/or major tranquilizers), additional research is needed to differentiate the effect of the disease from the effect of the drugs themselves [6].

Further, because protein oxidation in the lens is suspected as a major cause of cataracts, any phenomena that contribute to lens protein oxidation could be potential causes. In particular, vitreous liquefaction from its normal gel structure allows for greater transport of oxygen through the vitreous to the normally oxygen-starved lens, and could be a contributing factor to cataracts [7]. Since the vitreous in many people tends to liquefy with age, vitreous liquefaction may be a confounding factor with age. Additionally, vitreous removal (vitrectomy) and replacement by liquid is manytimes followed by cataracts, offering further evidence for enhanced oxygenation of the protein in the lens through the liquid.

There are also congenital cataracts, where some babies are born with cataracts or develop them in childhood, often in both eyes [8]. Additionally, there are secondary cataracts, which develop primarily as a result of another disease occurrence in the body (e.g., diabetes). Secondary cataract development has also been linked to steroid use. Finally, there are traumatic cataracts, whereby eye(s) that have sustained an injury may develop a traumatic cataract either immediately following the incident, or several years later [9].

Alternatively, one can define the different types of cataracts according to the cataract location on the eye lens. Nuclear cataract is the most common type of cataract, and the most common type associated with aging. Nuclear cataracts develop in the center of the lens and can induce myopia, or

nearsightedness - a temporary improvement in reading vision which is sometimes referred to as "second sight." Cortical cataract initially develops as wedge-shaped spokes in the cortex of the lens, with the spokes extending from the outside of the lens to the center. When these spokes reach the center of the lens they interfere with the transmission of light and cause glare and loss of contrast. This type of cataract is frequently developed in persons with diabetes, and while it usually develops slowly, it may impair both distance and near vision so significantly that surgery is often suggested at an early stage. Subcapsular cataract usually starts as a small opacity under the capsule, at the back of the lens. This type of cataract develops slowly and significant symptoms may not occur until the cataract is well developed. A subcapsular cataract is often found in persons with diabetes, myopia, retinitis pigmentosa, and in those taking steroids [10].

#### **1.4. Approach**

The generic ODS LRD approach is similar to that used for attacking the RP problem, was described in Chapter 2 (also see [3]), and will not be repeated. The specific approach used does have substantial differences from the specific RP approach, and the specific steps employed are outlined in Chapter 2. The specific details of these steps are as follows.

##### **1.4.1. Core Cataracts Literature**

The MEDLINE database was used, since we wanted to take advantage of the time-saving capabilities afforded by its MeSH taxonomy. The database range was 1995 to mid-2007. The first step involved retrieving the core cataracts literature. We used the single word 'cataract\*' (both as a text word and MeSH term) as a query to retrieve the core cataracts literature, and obtained 16853 records. While our previous queries for other disciplines (in non-LRD studies) have ranged up to hundreds of terms, the query 'cataract\*' was somewhat unique in that this one term was adequate for comprehensive retrieval. The **unrestricted** core cataracts literature retrieved as above was not limited to semantic classes.

We then retrieved the core cataracts literature restricted to the following semantic classes (125 records): (PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR ALGAE OR NUTS OR "DAIRY PRODUCTS" OR

FATS). These are categories extracted from the MeSH list, although they were entered in the query as text terms as well. While the concepts in this specific core cataracts literature are not discovery (by definition, they are associated with cataracts), they nevertheless show the types of substances/lifestyle practices that the potential discovery could provide.

Some illustrative examples are presented in results section 1.5.1. A more comprehensive list of examples obtained using a larger number of semantic classes is presented in Appendix 13.

#### **1.4.2. Directly Related Literature**

With use of our CLUTO document clustering software [11], we grouped the retrieved records from the unrestricted cataracts core literature into main categories that characterize the cataracts core literature. We then generated key phrases for each category to form 1) a query for retrieving the literature related directly to the core cataracts literature not restricted to semantic classes (6791 records retrieved), and 2) a query for retrieving the literature related directly to the core cataracts literature restricted to semantic classes (241 records retrieved). The latter query was as follows:

```
((("PROTEIN AGGREGATION" OR "PROTEIN AGGREGATES" OR
"PROTEIN DEGRADATION" OR "PROTEIN GLYCATION" OR
"PROTEIN OXIDATION")
NOT
CATARACT*)
AND
(PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT
EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR
PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR
ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS))
```

The first group of terms represents the biomedical phenomena that characterize the main thrusts of the cataract core literature (essentially degradation of the lens protein), the term ‘cataract\*’ insures that the records retrieved will be disjoint from the core cataracts literature, and the third group of terms represents the semantic classes from which potential discoveries could be drawn. The terms were used to search the text fields and the MeSH field. The records were retrieved, and examined for potential

discovery. Some examples of potential discovery are shown in sub-section 1.5.2 of the Results section

### 1.4.3. Indirectly Related Literature

The potential discovery examples listed in section 1.5.2 reflect the directly related literature. To obtain potential discovery from the indirectly related literature, the following steps were taken. The directly related literature (above) was clustered, and the main medical thrusts were identified. These thrusts included: Oxidative Stress; Lipid Peroxidation; Free Radical Scavengers; Oxidation-Reduction; Reactive Oxygen Species; “Oxidation Damage”. In this specific case, these ‘thrusts’ could be viewed as variants of an oxidation thrust.

In parallel, the potential discovery candidate records from the directly related literature were examined for textual patterns especially compared to textual patterns from the non-discovery records. *We observed that the non-discovery records typically contained one of the main thrusts as a MeSH term (sometimes none), whereas the potential discovery candidates typically contained two or more of the main thrusts as MeSH terms (and as text terms as well).* However, the combinations were intra-oxidation groupings.

We then selected the six leading thrust phrases shown above, and used them as the biomedical phenomena component of two test queries (with query structure similar to that of the one shown above). The biomedical phenomena component of the first query contained every combination of two MeSH terms possible from the six thrust phrases, along with the required constraints. A sampling showed there was a reasonable fraction of potential discovery candidates. Use of additional thrust phrases (highly recommended for adequately resourced studies) would have returned additional records and additional potential discovery candidates. Resource and time constraints precluded use of additional thrust phrases.

The biomedical phenomena component of the second query contained every combination of three MeSH terms possible from the six thrust phrases (twenty combinations:  $[6!/(3!*3!)]$ ; see [12]). This query, restricted to semantic classes, may be written in full as follows:



((OXIDATIVE STRESS AND LIPID PEROXIDATION AND (FREE RADICAL SCAVENGERS OR OXIDATION-REDUCTION OR REACTIVE OXYGEN SPECIES OR “OXIDATION DAMAGE”)) OR (OXIDATIVE STRESS AND FREE RADICAL SCAVENGERS AND (OXIDATION-REDUCTION OR REACTIVE OXYGEN SPECIES OR “OXIDATION DAMAGE”)) OR (OXIDATIVE STRESS AND OXIDATION-REDUCTION AND (REACTIVE OXYGEN SPECIES OR “OXIDATION DAMAGE”)) OR (OXIDATIVE STRESS AND REACTIVE OXYGEN SPECIES AND “OXIDATION DAMAGE”) OR (LIPID PEROXIDATION AND FREE RADICAL SCAVENGERS AND (OXIDATION-REDUCTION OR REACTIVE OXYGEN SPECIES OR “OXIDATION DAMAGE”)) OR (LIPID PEROXIDATION AND OXIDATION-REDUCTION AND (REACTIVE OXYGEN SPECIES OR “OXIDATION DAMAGE”)) OR (LIPID PEROXIDATION AND REACTIVE OXYGEN SPECIES AND “OXIDATION DAMAGE”) OR (FREE RADICAL SCAVENGERS AND OXIDATION-REDUCTION AND (REACTIVE OXYGEN SPECIES OR “OXIDATION DAMAGE”)) OR (FREE RADICAL SCAVENGERS AND REACTIVE OXYGEN SPECIES AND “OXIDATION DAMAGE”) OR (OXIDATION-REDUCTION AND REACTIVE OXYGEN SPECIES AND “OXIDATION DAMAGE”))

NOT

((("PROTEIN AGGREGATION" OR "PROTEIN AGGREGATES" OR "PROTEIN DEGRADATION" OR "PROTEIN GLYCATION" OR "PROTEIN OXIDATION") NOT CATARACT\*) OR CATARACT\*))

AND

(PLANTS, MEDICINAL OR PLANTS, EDIBLE OR PLANT EXTRACTS OR PLANT OILS OR PHYTOTHERAPY OR FRUIT OR FISH OIL OR FLAVONOIDS OR DIETARY SUPPLEMENTS)

This query was used to retrieve records related indirectly to the core cataracts literature. The first group of terms represents the biomedical phenomena reflected in the combinations of three MeSH terms. In some sense, **the biomedical phenomena combinations component can be viewed as a filter that targets potential discovery candidates more precisely, based on patterns associated with previously-identified potential discoveries.** It should not be viewed as similar to Swanson’s first numerical ranking condition (highest priority given to impacts along multiple pathways), since Swanson’s condition is inter-thrust (multiple disciplines), whereas the condition above is intra-oxidation. Whether this combination approach

above also filters out potential discovery remains to be seen. For the present demonstration study, filtering out discovery through term combinations was not an issue, since we obtained large amounts of potential discovery.

The second group of terms insures that the indirectly related literatures will be disjoint from both the directly related literature and the cataract core literature. Finally, the third group of terms represents the semantic classes from which potential discoveries would be drawn. It was modified from the semantic classes in the previous query (directly related literature) by examining the MeSH terms in the retrieved records from the directly related literature that were rated high for potential discovery, and observing the span of semantic classes accessed.

The query for indirectly related literatures unrestricted to semantic classes returned 16710 records, and the query for indirectly related literatures restricted to semantic classes returned 2036 records. After the restricted query for indirectly related literatures (above) was inserted into the PubMed search engine, the 2026 indirectly related literature records retrieved were sampled for potential discovery. Some examples of potential discovery from the indirectly related literature are shown in Results section 1.5.3.

## **1.5 Results**

This section contains representative examples of potential discovery from literatures related directly and indirectly to the core cataracts literature. Before proceeding to analyses, we present a few illustrative examples from the core cataracts literature restricted to semantic classes. While these are not discovery, they nevertheless reflect the types of impact that the non-drug approaches could potentially have for delaying or preventing the onset of cataracts.

### **1.5.1. Non-Drug Concepts in the Core Cataracts Literature**

1. “Periodic slit-lamp microscope examination indicated that in combination with vitamin-E, 0.01% curcumin (G-IV) delayed the onset and maturation of galactose-induced cataract. Biochemical analyses revealed that combined treatment of 0.01% **curcumin and vitamin-E diet** exhibited an efficient antioxidant effect, as it inhibited lipid peroxidation and contributed to a distinct rise in reduced glutathione content. The results indicate that **natural dietary ingredients are effective in combination rather than the individual**

administration as they are complementing each other in reducing the risk of galactose induced cataract.” [13].

[This example validates the thesis that will be re-iterated throughout this monograph: combinations of potential discoveries (synergies) may also be considered as potential discovery.

1a. “Regular consumption of fruit and vegetables is associated with reduced risks of cancer, cardiovascular disease, stroke, Alzheimer disease, cataracts, and some of the functional declines associated with aging.....We propose that the additive and synergistic effects of phytochemicals in fruit and vegetables are responsible for their potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruit and vegetables is attributed to the complex mixture of phytochemicals present in whole foods.” [14].

[Further validation of the synergistic combination thesis].

2. “IH636 grape seed proanthocyanidin extract effectively suppressed cataract formation in rats. Routine consumption of grape seed proanthocyanidin extract in the form of food or dietary supplement may offer a prophylactic measure against onset and progression of cataract.” [15].

3. “...a low-carbohydrate diet plus Pinus maritima may be an effective antioxidant and antihyperglycemic therapy, reducing the risk of diabetic retinopathy and cataract formation.” [16]

4. “The aim of the present paper is to investigate whether a vegetal extract, wheat sprout extract (WESPRESS), could mimic the thymus action on recovering age-related alterations and if this extract can cure an age-associated pathology, the cataract in dogs ..... Old dogs were orally treated for a month and the lens opacity analysed before and after the treatment. Results showed a reduction from 25 to 40% of lens opacity.” [17].

5. “...the OXYS rat strain is the useful model for macular degeneration and senile cataract and long-term supplementation with [Bilberry Extract] is effective in prevention of macular degeneration and cataract.” [18].

6. “Hazelnut prevented doxorubicin-induced cataract in low doses. Since it has no known harmful effect on healthy cells, it may be beneficial in humans.” [19].

7. “**Ocimum sanctum** modulates selenite-induced cataractogenic changes and prevents rat lens opacification.” [20].
8. “**Aralia extract** inhibits aldose reductase and acts in vitro as an antioxidant, and suggests that these activities have a preventive effect on cataractogenesis in xylose containing lens organ cultures and in in vivo in STZ induced diabetic rats.” [21].
9. “**Lycopene** protects against experimental cataract development by virtue of its antioxidant properties, and it may be useful for prophylaxis or therapy against cataracts.” [22].

### **1.5.2. Non-Drug Concepts in the Directly Related Literature**

1. “... detailed analyses of intracellular oxidative stress and protein oxidation suggest that **isogentisin** promotes cell survival by activating cellular repair functions.” [23].
2. “The extracts of **Cordyceps sinensis (CSE)** and **Cordyceps militaris (CME)** are well-known for their biological effects. In the present study, the antioxidant efficiency of CME and CSE in protecting lipid, protein, and low-density lipoprotein (LDL) against oxidative damage was investigated..... On the basis of the results obtained, the protective effects of CME and CSE against oxidative damage of biomolecules are a result of their free radical scavenging abilities.” [24].
3. “Wen-Pi-Tang, an Oriental medical prescription composed of **Rhei Rhizoma**, Ginseng Radix, Aconiti Tuber, Zingiberis Rhizoma and Glycyrrhizae Radix, is used clinically as a medicine to treat renal failure. This study was conducted to examine the inhibitory activity of the five crude drug components of Wen-Pi-Tang and several pure compounds isolated from Rhei Rhizoma and Glycyrrhizae Radix against the protein glycation reaction. **Rhei Rhizoma** exerted the most potent activity, Zingiberis Rhizoma and Glycyrrhizae Radix showed relatively moderate activity ....” [25].
4. “The whole extract of the fresh berries of **Hippophae rhamnoides L.** (RH-3) ..... was investigated for its effects on mitochondria isolated from mouse liver..... This study suggests that pre-irradiation treatment of mice

with RH-3 protects the functional integrity of mitochondria from radiation-induced oxidative stress.” [26].

5. “..... in the presence of this lipid algae extract [(*Phaeodactylum tricornutum*) RNK], the level of oxidized proteins is reduced, as assessed by the Oxyblot technique..... Altogether, these results argue for the presence of compounds in this algae extract that have a stimulating and/or protective effect on proteasome activity, resulting in a decreased level of protein oxidation.” [27].

6. “The present study reports the protective effects of *kolaviron*, a Garcinia biflavonoid from the seeds of *Garcinia kola* widely consumed in some West African countries, against oxidative damage to molecular targets ..... kolaviron exhibits protective effects against oxidative damage to molecular targets via scavenging of free radicals and iron binding.” [28].

### **1.5.3. Non-Drug Concepts in the Indirectly Related Literature**

1. “Walnut (*Juglans regia L.*) bark contains several therapeutically active constituents, especially polyphenols. *Walnut bark extract* treatment resulted in protective restoration of decreased antioxidants in [cyclophosphamide]-treated animals. Administration of extract restored all the antioxidants significantly and lowered the elevated LPO in the bladder. A correlation between radical scavenging capacities of the extract with phenolic content was observed thus justifying its antioxidant potential against oxidative stress-mediated urotoxicity in mice.” [29].

2. “These results clearly demonstrate the role of oxidative stress and its relation to renal disfunctioning and suggest a protective effect of A. *[Acorus] calamus* on NiCl<sub>2</sub>-induced nephrotoxicity in a rat experimental model.” [30].

3. “From a disease-prevention perspective, recent progress in phytochemical and nutraceutical research clearly suggests benefits outweigh the risk pattern. Although powerful antioxidant properties have been the most acclaimed mechanism of action for these entities, the individual antioxidants studied in clinical trials do not appear to have consistent preventative effects. The actions of the antioxidant nutrients alone do not explain the observed health benefits of diets rich in fruits and vegetables for chronic diseases. Therefore, we proposed that the *additive and synergistic effects of*

*phytochemicals in fruits and vegetables are responsible for these potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruits and vegetables is attributed to the complex mixture of phytochemicals present in plants* [1]. Surprisingly, however, no studies have attempted to evaluate the combined antitoxic potential of a phytochemical-nutraceutical mixture (PNM) in in vivo models. Therefore, this study, for the first time, was designed to investigate whether pre-exposure to a unique PNM has the ability to impede mechanistic events involved in acetaminophen (APAP)-induced hepatotoxicity. Besides several vitamins and minerals in balanced proportions (approximately US RDA), the PNM used in this investigation contained several well-known phytochemicals such as citrus flavonoids, red wine polyphenols, Garcinia, Gymnema, Ginkgo, Ephedra sinica, Camellia sinensis, Silybum, Guarana, Eluthero, Allium sativum and Ocimum basilicum extracts..... our investigation suggests that a *mixture containing an assortment of phytochemicals/nutraceuticals may serve as a much more powerful blend in preventing drug or chemical-induced organ injuries than a single phytochemical or nutraceutical entity.*” [31].

**[The importance of this article is that it shows the combination of known anti-oxidants provides a synergistic, more predictable effect, and is further validation of our thesis that combinations of potential discoveries may also be considered as a discovery.**

4. “It is concluded that Z. Clinopoides [*Ziziphora clinopoides*] inhibits acetic acid toxic reactions in the mouse bowel through inhibition of cellular oxidative stress.” [32].

5. “*Gypenosides* (GPs) were tested for their ability to protect primary cultures of immature cortical cells against oxidative glutamate toxicity..... We conclude that GPs protect cortical cells by multiple antioxidative actions via enhancing intracellular GSH, suppressing glutamate-induced cytosolic Ca(2+) elevation and blocking glutamate-induced apoptosis.” [33].

6. “An extract of the medicinal plant, *Biophytum sensitivum* (L.) DC (Oxalidaceae), was evaluated for its antioxidant potential ..... The results of this study indicate that B. sensitivum has significant antioxidant activity both in vitro and in vivo.” [34].

7. “.....the antioxidant potential of ethanolic extract of E. *[eruca] sativa* seeds was determined ..... E. sativa seeds possess a potent antioxidant and

renal protective activity and preclude oxidative damage inflicted to the kidney.” [35].

#### **1.5.4. Discussion of Results**

##### **1.5.4.1. Magnitude of Results**

Because the purpose of the cataracts study was to demonstrate an approach, and not necessarily to be comprehensive, a number of shortcuts were taken:

- Not all possible semantic categories for potential discoveries were identified, only the most obvious.
- Relatively few terms were selected for both the direct and indirect queries; many more were available.
- Not all retrieved records were examined; only enough to demonstrate the quality of results.
- The potential expansion to indirectly related literatures using citation linking described previously was not done.

Thus, the results obtained should be viewed as the tip of a very large iceberg.

Nevertheless, we estimate that hundreds of potential discoveries were generated by our streamlined approach, the majority of which derived from the indirectly related literature. This volume of potential discovery is of the same order of magnitude (if not greater) as in the RP study.

##### **1.5.4.2. Vetting of Results**

During the vetting process, a number of potential discovery candidates had to be eliminated due to their presence in the core literature. We found that almost all of the pre-vetted potential discovery candidates that eventually appeared in the cataracts core literature were relatively high frequency concepts (e.g., green tea, grape seed extract, puererin, curcumin, etc). Obviously, a large amount of research on these substances in areas related to the cataract problem (e.g., oxidation) almost insures that there will be some spillover into cataracts research. This is further confirmation of our hypothesis that high frequency concepts militate against discovery, and that it is the low frequency concepts that offer the greatest promise for discovery.

Unfortunately, most of the ODS LRD techniques in existence today appear to be dependent on high frequency phenomena.

Eliminating prior discoveries through the vetting process is not a major problem. More serious is that non-indexed (relatively recent Medline records) or non-properly indexed records [36] are not available for discovery using MeSH alone. To overcome this limitation, some type of text access query would be necessary. We overcame this limitation partially since all our search terms were text phrases as well as MeSH terms, and could access non-MeSH text fields. A more comprehensive hybrid text-MeSH technique will be developed in our next round of discovery studies.

## 1.6 Conclusions

The picture from the potential discoveries listed (and the hundreds of additional potential discoveries possible with a properly resourced study) is a synergy of lifestyle/dietary practices that could be interpreted as ***anti-cataract***. More laboratory tests and field trials would have to be done on all these items to insure that they are anti-cataract and safe, but these preliminary literature-based results offer some promise of what is possible.

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## **Chapter 5 - LITERATURE-RELATED DISCOVERY: POTENTIAL TREATMENTS FOR PARKINSON'S DISEASE**

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### **1.1 Overview of Study**

The previous two chapters described the first two medical studies we performed using LRD. Chapter 3 described the manually intensive RP study (also see [1]), and Chapter 4 described the streamlined cataracts study (also see [2]). The present chapter presents a streamlined yet comprehensive approach for systematic acceleration of discovery, and demonstrates the generation of large amounts of potential discovery for treatment of PD. The definitions of discovery and innovation and the approach background were shown in Chapter 1 (see also [3]), and the approach methodology was shown in Chapter 2 (also see [4]). The present chapter provides an overview of the etiology and treatment of PD, then proceeds to retrieve and analyze the core PD literature, and literatures related directly and indirectly to the core PD literature. These related literatures contain the seeds of potential discovery for PD, and some examples of potential discovery are presented for both classes of related literatures. Also, examples of interesting but non-discovery concepts from the core PD literature are presented, since they have practical value in their own right.

### **1.2. Purpose of Study**

We selected the subject of PD because of its global prevalence, and its apparent intractability to all treatments except for palliative remediation mainly through drugs or surgery. Our main goal was to identify non-drug non-surgical treatments that would 1) prevent the occurrence, or 2) reduce the progression rate, or 3) stop the progression, or 4) maybe even reverse the progression, of PD. A second goal was to demonstrate that we could again solve an ODS LRD problem with no prior knowledge of any results or prior work (unlike the case of the RP problem). Before proceeding to describe our approach and results, we summarize the medical issues and mainline treatments for PD.

### **1.3. Parkinson's Disease Background**

PD develops as a part of the brain known as the substantia nigra degenerates. [5]. The substantia nigra is located halfway between the cerebral cortex and the spinal cord. In healthy people, the substantia nigra contains nigral nerve cells that produce the chemical dopamine. Dopamine travels along nerve cell pathways from the substantia nigra to the striatum. In the striatum, dopamine activates nerve cells that coordinate normal muscle activity. In people with PD, nigral cells deteriorate and die at an accelerated rate, and the loss of these cells reduces the supply of dopamine to the striatum. Without adequate dopamine, nerve cells of the striatum activate improperly, impairing a person's ability to control movement [6] Additionally, collections of proteins (Lewy bodies, a sign of nerve cell death) form in the nerve cells [7]

Dopamine and acetylcholine are two neurotransmitters in the brain that affect motor control. When there is reduced dopamine, the dopamine-acetylcholine imbalance makes motor control more difficult, and produces the symptoms of PD. Most of the mainline drug therapies are aimed at restoring this balance. This can be done by increasing the amount of dopamine secreted from the remaining cells, reducing the secretion of acetylcholine, or some combination of the two [8].

The main drug treatment, Levodopa, enters the brain where it transforms into dopamine. Unfortunately, when L-Dopa is taken alone, about 95% of it is metabolized by other parts of the body before it reaches the brain, causing numerous adverse side effects. Other drugs taken with L-Dopa allow more L-Dopa to enter the brain before it converts to dopamine [9].

In early stages of PD, dopamine agonists, which mimic the action of dopamine by activating nerve cells in the striatum, are used alone to minimize the adverse side effects of L-Dopa, but in later PD stages may be used in combination with L-Dopa and other drugs. Anticholinergics block the action of acetylcholine, and can be used in early PD to lessen tremor and drooling, but tend not to be effective in treating bradykinesia or posture instability. Many other types of specific drugs are used; none stop the progression of PD, although early symptom control is possible [10]

Two similar surgical procedures (thalamotomy and pallidotomy) destroy regions of the brain that produce the uncontrolled spasmodic movements in PD patients [11]. A more recent procedure, deep brain stimulation, sends electricity through a probe to normalize electrical activity in the brain region, reversing the symptoms of PD [12].

More experimental procedures include transplant of dopamine-producing cell tissue into the brain, use of human stem cells that can be manipulated to become dopamine-producing cells, [13], and gene transfer (inserting a gene that produces dopamine into the brain cells) [14].

All of the above approaches address PD symptoms only (not causes), have side effects ranging from moderate to severe, and eventually lose their impact. They are ‘magic bullet’ types of approaches, and, at a minimum, need to be supplemented by the anti-PD lifestyle that will be implied by our findings.

## **1.4. Approach**

The specific approach used was similar to what we used for the cataracts problem, with the exception that phrase combining was used to determine the directly related literature query in addition to the indirectly related literature query. The approach was outlined in Chapter 2 (also see [4]), and the specific steps employed were as follows.

### **1.4.1. Core PD Literature**

The MEDLINE database was used, since we wanted to take advantage of the time-saving capabilities afforded by its MeSH taxonomy. The first step involved retrieving the core PD literature. We used the single words (Parkinson\* NOT (Parkinson\* [AU] OR Wolff-Parkinson)) as a query to retrieve the core PD literature, where these words served as both text words and MeSH terms. Over the time period 1990-2007, we retrieved 30110 records total (with and without Abstracts) (April 2007).

### **1.4.2. Directly Related Literature**

With use of our CLUTO document clustering software [15], which groups only those records that contain Abstracts, we grouped the retrieved records (PD core literature) into main categories that characterize the PD core literature. We then generated key phrases for each category to form a query for retrieving the literature related directly to the core PD literature.

It was observed that records most relevant to potential discovery tended to have more than one of the key query mechanism terms (identified from the

clusters) in the MeSH field. Therefore, to reduce the number of retrieved records to a more manageable level, the query was re-written to include only combinations of two of the query mechanism terms. Selection of combinations of two was a compromise between the overly comprehensive zero combination case and the possibly over-restrictive combination of three or more terms cases.

Some of the combinations of terms are inter-medical thrust; the combination crosses medical disciplines. The PD study was the only one of our 'streamlined' studies in which the query term combinations in the combinatorial process were inter-discipline. A more detailed post facto evaluation of the potential discovery candidates that served as the source of the terms used in the combinations for all the 'streamlined' medical studies showed that the records contained mainly intra-disciplinary combinations. Subsequent queries reflected this intra-discipline emphasis, and did not include inter-discipline combinations. Any records that include inter-disciplinary effects can still be retrieved, since they are not excluded by the intra-discipline form of the query.

The form of this query restricted to non-drug semantic classes was as follows:

((("PROTEIN AGGREGATION" AND "PROTEIN AGGREGATES") OR ("PROTEIN AGGREGATION" AND "PROTEIN DEGRADATION") OR ("PROTEIN AGGREGATION" AND "PROTEIN OXIDATION") OR ("PROTEIN AGGREGATION" AND "LEWY BODIES") OR ("PROTEIN AGGREGATION" AND "ALPHA SYNUCLEIN") OR ("PROTEIN AGGREGATION" AND "OXIDATIVE STRESS") OR ("PROTEIN AGGREGATION" AND ("MONAMINE OXIDASE" AND INHIBIT\*)) OR ("PROTEIN AGGREGATION" AND PARKIN) OR ("PROTEIN AGGREGATION" AND UBIQUITIN) OR ("PROTEIN AGGREGATION" AND "TAU PROTEIN") OR ("PROTEIN AGGREGATION" AND "AMYLOID PRECURSOR PROTEIN") OR ("PROTEIN AGGREGATES" AND "PROTEIN DEGRADATION") OR ("PROTEIN AGGREGATES" AND "PROTEIN OXIDATION") OR ("PROTEIN AGGREGATES" AND "LEWY BODIES") OR ("PROTEIN AGGREGATES" AND "ALPHA SYNUCLEIN") OR ("PROTEIN AGGREGATES" AND "OXIDATIVE STRESS") OR ("PROTEIN AGGREGATES" AND ("MONAMINE OXIDASE" AND INHIBIT\*)) OR ("PROTEIN AGGREGATES" AND PARKIN) OR ("PROTEIN AGGREGATES" AND UBIQUITIN) OR



(“PROTEIN AGGREGATES” AND “TAU PROTEIN”) OR (“PROTEIN AGGREGATES” AND “AMYLOID PRECURSOR PROTEIN”) OR (“PROTEIN DEGRADATION” AND “PROTEIN OXIDATION”) OR (“PROTEIN DEGRADATION” AND “LEWY BODIES”) OR (“PROTEIN DEGRADATION” AND “ALPHA SYNUCLEIN”) OR (“PROTEIN DEGRADATION” AND “OXIDATIVE STRESS”) OR (“PROTEIN DEGRADATION” AND (“MONAMINE OXIDASE” AND INHIBIT\*)) OR (“PROTEIN DEGRADATION” AND PARKIN) OR (“PROTEIN DEGRADATION” AND UBIQUITIN) OR (“PROTEIN DEGRADATION” AND “TAU PROTEIN”) OR (“PROTEIN DEGRADATION” AND “AMYLOID PRECURSOR PROTEIN”) OR (“PROTEIN OXIDATION” AND “LEWY BODIES”) OR (“PROTEIN OXIDATION” AND “ALPHA SYNUCLEIN”) OR (“PROTEIN OXIDATION” AND “OXIDATIVE STRESS”) OR (“PROTEIN OXIDATION” AND (“MONAMINE OXIDASE” AND INHIBIT\*)) OR (“PROTEIN OXIDATION” AND PARKIN) OR (“PROTEIN OXIDATION” AND UBIQUITIN) OR (“PROTEIN OXIDATION” AND “TAU PROTEIN”) OR (“PROTEIN OXIDATION” AND “AMYLOID PRECURSOR PROTEIN”) OR (“LEWY BODIES” AND “ALPHA SYNUCLEIN”) OR (“LEWY BODIES” AND “OXIDATIVE STRESS”) OR (“LEWY BODIES” AND (“MONAMINE OXIDASE” AND INHIBIT\*)) OR (“LEWY BODIES” AND PARKIN) OR (“LEWY BODIES” AND UBIQUITIN) OR (“LEWY BODIES” AND “TAU PROTEIN”) OR (“LEWY BODIES” AND “AMYLOID PRECURSOR PROTEIN”) OR (“ALPHA SYNUCLEIN” AND “OXIDATIVE STRESS”) OR (“ALPHA SYNUCLEIN” AND (“MONAMINE OXIDASE” AND INHIBIT\*)) OR (“ALPHA SYNUCLEIN” AND PARKIN) OR (“ALPHA SYNUCLEIN” AND UBIQUITIN) OR (“ALPHA SYNUCLEIN” AND “TAU PROTEIN”) OR (“ALPHA SYNUCLEIN” AND “AMYLOID PRECURSOR PROTEIN”) OR (“OXIDATIVE STRESS” AND (“MONAMINE OXIDASE” AND INHIBIT\*)) OR (“OXIDATIVE STRESS” AND PARKIN) OR (“OXIDATIVE STRESS” AND UBIQUITIN) OR (“OXIDATIVE STRESS” AND “TAU PROTEIN”) OR (“OXIDATIVE STRESS” AND “AMYLOID PRECURSOR PROTEIN”) OR ((“MONAMINE OXIDASE” AND INHIBIT\*) AND PARKIN) OR ((“MONAMINE OXIDASE” AND INHIBIT\*) AND UBIQUITIN) OR ((“MONAMINE OXIDASE” AND INHIBIT\*) AND “TAU PROTEIN”) OR ((“MONAMINE OXIDASE” AND INHIBIT\*) AND “AMYLOID PRECURSOR PROTEIN”) OR (PARKIN AND UBIQUITIN) OR (PARKIN AND “TAU PROTEIN”) OR (PARKIN AND “AMYLOID PRECURSOR PROTEIN”) OR (UBIQUITIN

AND "TAU PROTEIN") OR (UBIQUITIN AND "AMYLOID  
 PRECURSOR PROTEIN") OR ("TAU PROTEIN" AND "AMYLOID  
 PRECURSOR PROTEIN") OR ((RECEPTOR\* AND (DOPAMINE OR  
 ANTAGONIST OR NMDA OR AGONIST)) AND MPTP) OR  
 ((RECEPTOR\* AND (DOPAMINE OR ANTAGONIST OR NMDA OR  
 AGONIST))AND (CELL\* AND APOPTOSIS)) OR ((RECEPTOR\* AND  
 (DOPAMINE OR ANTAGONIST OR NMDA OR AGONIST)) AND  
 (MITOCHONDRIA\* AND (IMPAIR\* OR DYSFUNCTION OR  
 SUPPRESSION OR BLOCKAGE\*))) OR ((RECEPTOR\* AND  
 (DOPAMINE OR ANTAGONIST OR NMDA OR AGONIST)) AND  
 (DOPAMIN\* AND NEUTRON\*)) OR ((RECEPTOR\* AND (DOPAMINE  
 OR ANTAGONIST OR NMDA OR AGONIST)) AND "DOPAMINE  
 INHIBIT\*") OR (MPTP AND (CELL\* AND APOPTOSIS)) OR (MPTP  
 AND (MITOCHONDRIA\* AND (IMPAIR\* OR DYSFUNCTION OR  
 SUPPRESSION OR BLOCKAGE\*))) OR (MPTP AND (DOPAMIN\* AND  
 NEUTRON\*)) OR (MPTP AND "DOPAMINE INHIBIT\*") OR ((CELL\*  
 AND APOPTOSIS) AND (MITOCHONDRIA\* AND (IMPAIR\* OR  
 DYSFUNCTION OR SUPPRESSION OR BLOCKAGE\*))) OR ((CELL\*  
 AND APOPTOSIS) AND (DOPAMIN\* AND NEUTRON\*)) OR ((CELL\*  
 AND APOPTOSIS) AND "DOPAMINE INHIBIT\*") OR  
 ((MITOCHONDRIA\* AND (IMPAIR\* OR DYSFUNCTION OR  
 SUPPRESSION OR BLOCKAGE\*)) AND (DOPAMIN\* AND  
 NEUTRON\*)) OR ((MITOCHONDRIA\* AND (IMPAIR\* OR  
 DYSFUNCTION OR SUPPRESSION OR BLOCKAGE\*)) AND  
 "DOPAMINE INHIBIT\*") OR ((DOPAMIN\* AND NEUTRON\*) AND  
 "DOPAMINE INHIBIT\*")) NOT (PARKINSON\* NOT  
 (PARKINSON\*[AU] OR WOLFF-PARKINSON\*))  
 AND  
 (PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT  
 EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR  
 PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR  
 ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR  
 FLAVONOIDS OR "DIETARY SUPPLEMENTS")

The first group of terms represents the biomedical phenomena that comprise the main thrusts of the PD core literature (essentially idiopathic degradation of dopamine-producing cells in the substantia nigra and presence of Lewy bodies (excessive protein aggregations) in the dopaminergic neurons), the second (negation) group of terms '(Parkinson\* Not (Parkinson\*[AU] Or Wolff-Parkinson\*))' insures that the records retrieved will be disjoint from

the core Parkinson's Disease literature, and the last group of terms represents the semantic classes from which potential discoveries could be drawn. The terms were used to search the text fields and the MeSH field, and 363 records were retrieved. If the query is written with uncombined biomedical phenomena terms, then over 14000 records are retrieved.

How are potential discovery candidates identified from these retrievals? For the 363 record retrieval, almost every record was a potential discovery candidate. This should not be surprising, since the combinations of two query mechanism terms serve as strong semantic filters. Much of the work required was in the vetting, and most of the concept exclusions came from the patent literature vetting.

But even the 14000+ retrieval had a high fraction of potential discovery candidates. We went down the list and identified potential discovery candidates, and then proceeded with the vetting process.

For an adequately resourced study, where many more records would be available for potential discovery, the discovery identification processes developed for the Water Purification study [Chapter 7; also see 16, 17] could be used. The Cluster Semantic Filtering (CSF) approach would, for example, cluster the 14000+ records above. Visual inspection of the cluster themes would identify those that appeared most promising, as was the case in the Water Purification study. Then, each record in the promising clusters would be examined for discovery potential. The Latent Semantic Indexing (LSI) [18] approach [Chapter 7; also see 16, 17] would start with interesting core records and identify records in the related literatures similar conceptually but with different terminology.

Some examples of potential discovery from the directly related literature (using the query with combined terms) are listed in the Results section. The query with uncombined terms was also used to generate a few additional potential discoveries. They are listed after the directly related literature potential discoveries mentioned above.

### **1.4.3. Indirectly Related Literature**

To obtain potential discovery from the indirectly related literature, the following steps were taken. The directly related literature (above) was clustered using CLUTO, and the main medical thrusts were identified from

the text phrases in each cluster's Abstracts. These key text phrases that comprised the main medical thrusts included:

AGONIST RECEPTOR; ANTAGONIST RECEPTOR; ANTIOXIDANT ENZYMES; ARYL HYDROCARBON RECEPTOR; (BAICALEIN OR BCL OR FLAVOPIRIDOL); CASPASES ; ("DOPAMINE NEURON\* OR "DOPAMINERGIC NEURON\*); DOPAMINE RECEPTORS; ENZYME INHIBITORS; ((ERK OR MEK) AND "MAP KINASE" AND INHIBIT\*); ESTROGEN RECEPTOR; GLUTATHIONE PEROXIDASE; HEAT SHOCK PROTEINS; MITOCHONDRIAL DYSFUNCTION; MITOCHONDRIAL MEMBRANE; MITOCHONDRIAL STRESS; MOTOR ACTIVITY; MPP INDUCED; MPTP; NERVE DEGENERATION; OXIDATIVE DAMAGE; PROTEASOME PATHWAY; PROTEIN CARBONYL\*; PROTEIN CATABOLISM; PROTEIN DEGRADATION; PROTEIN OXIDATION; PROTEIN SYNTHESIS; PROTEOLYTIC PATHWAY; RECEPTOR BINDING; RECEPTORS, NMDA; SUPEROXIDE DISMUTASE; THIOBARBITURIC ACID REACTIVE; UBIQUITIN.

In parallel, the potential discovery candidate records from the directly related literature were examined for textual patterns both in the Abstract text and in the MeSH terms, especially compared to textual patterns from the non-discovery records. We observed that the non-discovery records typically contained one of the key phrases as a MeSH term (sometimes none), whereas the potential discovery candidates typically contained two or more of the key phrases as MeSH terms (and as text terms as well). The following thirteen MeSH terms were identified as key medical phrases in the potential discovery candidate records:

AMYLOID BETA PROTEIN; ANTIOXIDANTS; APOPTOSIS; CELL DEATH; CELL SURVIVAL; ENZYME ACTIVATION; FREE RADICALS; LIPID PEROXIDATION; MITOCHONDRIA; NEUROPROTECTIVE AGENTS; OXIDATION-REDUCTION; OXIDATIVE STRESS; REACTIVE OXYGEN SPECIES.

We then generated a query that had a three-part structure similar to that of the query for the directly related literature. The first part of the new query consisted of two groups of mechanisms terms, connected by the OR Boolean. The first group of mechanisms terms included the key text phrases in each cluster's Abstracts (shown above). The second group of mechanisms terms included the thirteen MeSH terms that were found in

groups associated with the potential discovery candidates (also shown above). The text-based terms in the first mechanisms group were connected by the OR Boolean. The MeSH terms in the second mechanisms group were combined in all combinatorial groups of three (the members of each group of three were connected by the AND Boolean), and all the groups were linked by the OR Boolean. As stated before, the first group of mechanisms (text based) was linked to the second group of mechanisms (MeSH-based) by the OR Boolean.

The second of the three query parts consisted of the core PD query and the directly related literature query, connected to the first two query parts by the NOT Boolean to insure that the indirectly related literature would be disjoint from the core and directly related literatures. The last part of the new query for indirectly related literatures consisted of the same semantic classes as in the indirect literature query, and was connected to the first two parts of the query by the AND Boolean. This indirectly related literature query returned 14188 records. A sampling showed there was a reasonable fraction of potential discovery candidates. Use of additional medical thrust text or MeSH phrases would have returned additional records and additional potential discovery candidates. If time and resources for the study are at a premium, then the first group of mechanisms (text based) can be linked to the second group of mechanisms (MeSH-based) by the AND Boolean. This increases the precision of the retrieval, and reduces the size of the retrieval substantially.

The full indirectly related literature query can be found in Appendix 2 of this monograph. Some examples of potential discovery from the indirectly related literature retrieved by this query are shown in the Results section.

## **1.5. Results**

This section contains representative examples of potential discovery from literatures related directly and indirectly to the core PD literature. Before proceeding to analyses, we present a few illustrative examples from the core PD literature restricted to semantic classes. While these are not discovery, they nevertheless reflect the types of impact that the non-drug approaches could potentially have for delaying or preventing the onset of PD. In addition, as we will discuss later, some of these core examples are prime candidates for innovation.

For example, UCP4-mRNA expression is increased in brain cells of rats maintained on caloric restriction. Neural cells with increased levels of UCP4 exhibit reduced reactive oxygen species (ROS) production and decreased mitochondrial calcium accumulation. The UCP4-mediated shift in energy metabolism reduces ROS production and increases the resistance of neurons to oxidative and mitochondrial stress, providing antiaging and neuroprotective effects [19]. Side effects of caloric restriction, as exhibited in rodent and primate studies, are positive on many fronts, and include increased life span [20]. There is an accumulating body of evidence for the positive effects of caloric restriction on UCP4 and other coupling proteins in both the Parkinson's core and non-core literatures, yet we have seen no mention of this harmless supplement in any of the mainline reviews.

Appendix 6 contains a more comprehensive listing of articles from the core PD non-drug literature restricted to semantic classes. A larger number of non-drug semantic classes were used than in the present study, the 1367 records retrieved were grouped into sixteen clusters, and the themes and record titles for each cluster were generated.

### **1.5.1. Non-Drug Concepts in the Core PD Literature**

1. "A short period of *zinc deficiency (ZD)* in young adult mice greatly accelerated apoptosis among pre-B and pre-T cells by 50% to 300%..... In marked contrast to *suboptimal zinc, caloric restriction (CR)* which when initiated in younger mice delayed the onset of autoimmunity and immunosenescence. CR appeared to also slow the aging of mitochondria and, thereby, reduced the release of reactive oxygen species that damage cells." [21].
2. "Our recent studies have demonstrated that *green tea polyphenol (-)*-epigallocatechin-3-gallate (EGCG) exerts neuroprotective/neurorescue effects against B-amyloid toxicity and protects neuronal cells from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium ion (MPP+) and 6-hydroxydopamine in vitro, or from N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) induced nigral dopaminergic neuronal loss in mice" [22].
3. "We show that the minimizing effect of AR [*Asparagus racemosus*] extract on oxidative damage in addition to the elevation of GPx (glutathione

peroxidase) activity and GSH (reduced glutathione) content could eventually result in protective effect on the KA-induced excitotoxicity.” [23].

4. “These data demonstrate that vanillin effectively scavenges PON (peroxynitrate) in cell-free systems.” [24].

5. “In Guadeloupe, epidemiological data have linked atypical parkinsonism with fruit and herbal teas from plants of the Annonaceae family, particularly Annona muricata. These plants contain a class of powerful, lipophilic complex I inhibitors, the annonaceous acetogenins..... These data are compatible with the theory that annonaceous acetogenins, such as annonacin, might be implicated in the aetiology of Guadeloupean parkinsonism and support the hypothesis that some forms of parkinsonism might be induced by environmental toxins.” [25].

6. “These data suggest that dairy consumption may increase the risk of Parkinson's disease, particularly in men..... Of the four individual dairy items [milk, yogurt, cheese, ice cream], only milk intake was significantly associated with a higher risk of Parkinson's Disease.” [26].  
(Since the data for this study came from questionnaires, the conclusions are probably limited to non-organic non-fermented pasteurized cow's milk, the milk consumed most frequently in the USA. Whether these conclusions apply to other categories of milk (non-cow, raw, fermented, organic) cannot be determined at this time.)

7. “Inclusion of 2% BBE (dietary blueberry extract) in a custom chow diet significantly increased the survival of implanted DA neurons and ameliorated rotational behavior asymmetries as compared to transplanted animals consuming a standard diet. These findings provide support for the potential of dietary phytochemicals as an easily administered and well-tolerated therapy that can be used to improve the effectiveness of DA neuron replacement.” [27].

8. “these results indicate that SF (sulforaphane) causes induction of QR1 gene expression, removal of intracellular DA quinone, and protection against toxicity in DAergic cells. Thus, this major isothiocyanate found in cruciferous vegetables may serve as a potential candidate for development of treatment and/or prevention of PD.” [28].

***(As shown by the following applications to cancer and cardiovascular problems, in addition to the potential PD application above, sulforaphane***

*may be a foundational substance for improved human health. Consumers of higher levels of Brassica vegetables, particularly those of the genus Brassica (broccoli, Brussels sprouts and cabbage), reduce their susceptibility to cancer at a variety of organ sites. Several studies have documented the cancer-preventive activity of a significant number of isothiocyanates, the most characterized of which is sulforaphane (SF). Additionally, a recent unpublished study concluded “Our results demonstrate, for the first time, that a number of endogenous antioxidants and Phase 2 enzymes can be induced in cultured cardiomyocytes by low micromolar concentration of [sulforaphane], and that this nutritional mediated upregulation of cellular defences is accompanied by a markedly increased resistance to cardiac cell injury elicited by peroxide”. Highest concentrations of SF are found in broccoli sprouts, but the concentrations are reduced under cooking.).*

9. “The highest radical-scavenging activity was found in ....Cimicifuga racemosa (black cohosh).” [29].

10. “In patients with T2DM, a HAGE [high advanced glycation endproducts] meal induces a more pronounced acute impairment of vascular function than does an otherwise identical LAGE [low advanced glycation endproducts] meal. Therefore, chemical modifications of food by means of cooking play a major role in influencing the extent of postprandial vascular dysfunction [increased concentrations of serum AGE and markers of endothelial dysfunction and oxidative stress].” [30].

### **1.5.2. Non-Drug Potential Discovery Concepts in the Directly Related Literature**

1. “On the basis of the results obtained, the protective effects of CME (Cordyceps militaris) and CSE (Cordyceps sinensis) against oxidative damage of biomolecules are a result of their free radical scavenging abilities.” [31].

2. “The results indicate that at physiological levels, beta-car, malanga carotenoids extract, and malanga leaf powder have antioxidant effects in rats.” [32]



3. “We suggest that *kolaviron* exhibits protective effects against oxidative damage to molecular targets via scavenging of free radicals and iron binding.” [33].
4. “HCA-SX [a novel calcium/potassium salt of (-)-hydroxycitric acid extracted from the *dried fruit rind of the plant Garcinia cambogia*] may be used as an intervention to overcome obesity-related complications, including inflammation, oxidative stress, and insulin resistance” [34].
5. “These results suggest that *isohumulones* may prevent the progression of renal injury caused by hypertension via an anti-oxidative effect.” [35].
6. “These results collectively demonstrated the usefulness of these polyphenolic compounds [*brown algae*] as fundamental chemopreventive agents against vascular risk factors originating from oxidative stress.” [36].
7. “The current investigation focuses attention on the neuroprotective and antioxidant properties of aqueous extracts from *Halimeda incrassata (Hi)* and *Bryothamnion triquetrum (Bt)*..... Some comments on the probable targets of the neuroprotection exerted by these two extracts are included in this paper.” [37].

### **1.5.3. Non-Drug Potential Discovery Concepts in the Indirectly Related Literature**

1. “The present study investigated the potential cytoprotective properties of a combination of plant extracts (KIOM-79) obtained from *Magnolia officinalis*, Pueraria lobata, Glycyrrhiza uralensis, and *Euphorbia pekinensis*, against the oxidative stresses induced by streptozotocin (STZ)..... these findings suggest that KIOM-79 protects against STZ induced cell death in RINm5F cells by inhibiting ROS generation and the ERK pathway.” [38].
2. “*G. [Gynandropsis] gynandra* extract was found to potentially diminish the rate of lipid peroxidation, with a significant increase in the levels of enzymatic (superoxide dismutase, catalase and glutathione peroxidase) and non-enzymatic (reduced glutathione vitamins E and C, and uric acid) antioxidants, which were found, altered during aflatoxin B1 (AFB1) injection. The result confirmed that G. gynandra extract exerts its chemopreventive efficacy by preventing the rate of lipid peroxidation and

influenced the enzymatic and non-enzymatic antioxidants in AFB1 induced male albino rats.” [39].

3. “JLHD [*Jianpi Liqui Huoxue Decoction*] has significant effects against alcoholic liver injury, the acting mechanism of which is likely to be related with its anti-lipid peroxidative effect.” [40].
4. “Protective effect of *Lycium barbarum polysaccharides* on streptozotocin-induced oxidative stress in rats.” [41].
5. “Our findings suggest that *M. [Marrubium] vulgare* provides a source of natural antioxidants, which inhibit LDL oxidation and enhance reverse cholesterol transport and thus can prevent cardiovascular diseases development. These antioxidant properties increase the anti-atherogenic potential of HDL.” [42].
6. “all the plant extracts statistically ( $P < 0.05$ ) reduced the production of TBARS in a concentration-dependent manner in all the tested pro-oxidant-induced oxidative stresses. *Alchornea cordifolia* appeared to offer the highest protection. The results of the present study suggest that the use of these plants in the treatment of various diseases, especially liver disease, is probably due to their ability to act as antioxidants” [43].
7. “Compound 2 [myricitrin-5-methyl ether] (*flavonoid* from the flower of *Rhododendron yedoense var. poukhanense*) showed high activity in both the inhibition of xanthine oxidase (1.1 +/- 0.21 mM) and in the activation of superoxide scavenging” [44].
8. “the results suggest that aqueous extract of *G. [Gongronema] latifolium*. Leaves possesses hypoglycemic as well as anti-lipid peroxidative properties.” [45].

Because the purpose of the PD study was to demonstrate an approach, and not necessarily to be comprehensive, a number of shortcuts were taken. Not all possible semantic categories for potential discoveries were identified, only the most obvious. Relatively few terms were selected for both the direct and indirect queries; many more were available. Not all retrieved records were examined; only enough to demonstrate the quality of results. The potential expansion to indirectly related literatures using citation linking

described previously was not done. Thus, the results obtained should be viewed as the tip of a very large iceberg.

Nevertheless, we estimate that hundreds of potential discoveries were generated by our streamlined approach, the majority of which derived from the indirectly related literature. This volume of potential discovery is of the same order of magnitude (if not greater) as in the RP study. As was the case with the cataracts literature, and for the same reasons, some of the potential discovery candidates had to be eliminated during the vetting process, when it was found that they appeared in the core PD literature.

## 1.6 Discussion

The picture from the handful of potential discoveries reported in this paper (and the hundreds of additional potential discoveries possible with a properly resourced study, including additional semantic classes such as Environmental) is a synergy of lifestyle/ dietary practices that could be interpreted as *anti-Parkinson*. Along with non-discovery items such as less dairy, green tea, caloric restriction, blueberries, broccoli/ broccoli sprouts, and lower temperature cooking are potential discovery items such as malanga extracts, kolaviron, isohumulones, brown algae, and Rhododendrum flavonoids. As stated above, more laboratory tests and field trials would have to be done on all these items to insure that they are anti-Parkinson and safe, but these preliminary literature-based results offer some promise of what is possible.

We are finding a major disconnect between the therapies presently or potentially available presented on all the major medical Web sites (and in PD mainstream journal review papers), and the therapies suggested by what has already been demonstrated in the core PD literature, much less what we have generated from the related literatures. The major medical Web sites (and journal reviews) present about a half-dozen drug treatment options for PD, and perhaps 3-4 surgical/ invasive procedures, as shown in the PD Background section. We have seen no major medical Web sites that even mention any of the non-drug approaches shown in the PD core results section. We believe the core literature and related literature potential discoveries and innovations have the potential to supplement the mainline medical treatments (if borne out by trials).



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## **Chapter 6 - LITERATURE-RELATED DISCOVERY: POTENTIAL TREATMENTS FOR MULTIPLE SCLEROSIS**

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### **1. Introduction**

#### **1.1 Overview**

Chapter 3 described the manually intensive LRD study for RP (also see [1]), Chapter 4 described the first streamlined ODS LRD approach applied to cataracts (also see [2]), and Chapter 5 presented the second streamlined LRD approach applied to PD (also see [3]). The present chapter presents an expansion of the streamlined yet comprehensive approach for systematic acceleration of potential discovery, and demonstrates the generation of large amounts of potential discovery for treatment of MS. The definitions of discovery and innovation and the approach background were shown in Chapter 1 (see also [4]), and the approach methodology was shown in Chapter 2 (see also [5]).

The present chapter provides an overview of the etiology and treatment of MS, then proceeds to retrieve and analyze the core MS literature, and literatures related directly and indirectly to the core MS literature. These related literatures contain the seeds of potential discovery for MS, and some examples of potential discovery are presented for both classes of related literatures. Also, examples of interesting but non-discovery concepts from the core MS literature are presented, since they have practical value in their own right.

#### **1.2 Purpose of Study**

MS is a progressive neurodegenerative disorder (typically preceded by periods of remission and relapse), affecting mainly people in their early-mid life. It is characterized by changes in sensation (hypoesthesia), muscle weakness, abnormal muscle spasms, or difficulty to move; difficulties with coordination and balance (ataxia); problems in speech (Dysarthria) or swallowing (Dysphagia), visual problems (Nystagmus, optic neuritis, or diplopia), fatigue and acute or chronic pain syndromes, bladder and bowel difficulties, cognitive impairment, or emotional symptomatology (mainly depression). We selected the subject of MS because of its global prevalence,

and its apparent intractability to all treatments except for palliative remediation mainly through drugs or surgery. Our main goal was to identify non-drug non-surgical treatments that would 1) prevent or delay the onset, or 2) reduce the progression rate, or 3) stop the progression, or 4) maybe even reverse the progression of MS. A second goal was to demonstrate that we could solve an ODS LRD problem with no prior knowledge of any results or prior work, and that we could use more elements of our flow chart process without decrementing our streamlined process [5] significantly. We used the MeSH taxonomy of MEDLINE to restrict potential discoveries to selected semantic classes. Before proceeding to describe our specific approach and results, we summarize the medical issues and mainline treatments for MS.

## 2. Multiple Sclerosis Background

### 2.1 Overview

MS (also known as disseminated sclerosis or encephalomyelitis disseminata) is a chronic, inflammatory, demyelinating disease that affects the central nervous system (CNS) [6]. MS can cause a variety of symptoms, including changes in sensation, visual problems, muscle weakness, depression, difficulties with coordination and speech, severe fatigue, cognitive impairment, problems with balance, overheating, and pain. MS will cause impaired mobility and disability in more severe cases [7].

MS may take several different forms, with new symptoms occurring either in discrete attacks or slowly accruing over time. Clinically, most patients present with a relapsing remitting course, which correlates initially with an inflammatory phase of the disease. Later, it becomes more of a neurodegenerative phase, called secondary progressive. Between attacks, symptoms may resolve completely, but permanent neurologic problems often persist, especially as the disease advances [8]. **MS currently does not have a cure. Several treatments are available that may slow the appearance of new symptoms, although these treatments have their own side-effects.**

MS affects an estimated 300,000 people in the United States and probably more than 1 million people around the world — including twice as many women as men [9]. Most people experience their first signs or symptoms between ages 20 and 40. A significantly higher incidence of the disease is found in the northernmost latitudes of the northern and the southern

hemispheres compared to southernmost latitudes. This observation is based on the incidence of the disease in Scandinavia, northern United States and Canada, as well as Australia and New Zealand [10].

## 2.2 Pathology

MS affects neurons, the cells of the brain and spinal cord that carry information, create thought and perception, and allow the brain to control the body. Surrounding and protecting some of these neurons is a fatty layer known as the myelin sheath, which helps neurons carry electrical signals. MS causes gradual destruction of myelin (demyelination) and transection of neuron axons in patches throughout the brain and spinal cord. The name MS refers to the multiple scars (or scleroses) on the myelin sheaths. This scarring causes symptoms that vary widely, depending upon which signals are interrupted.

Pathologically, MS is characterized by the presence of areas of demyelination and T-cell predominant perivascular inflammation in the brain white matter. Some axons may be spared from these pathological processes.

The severity of demyelination may be assessed by relative preservation or destruction of oligodendroglia. It is demonstrated that early in the course of the disease more oligodendroglia are preserved in the plaque; thus, some degree of remyelination remains possible. In other patients, there is a complete loss of oligodendroglia. In this group of patients, possibility of remyelination is dramatically decreased [11].

Whatever route the pathological process takes from inflammation to demyelination, the effects of myelin loss by the nerve fibers are quite dramatic. Saltatory conduction is much more energy efficient than nerve impulses transmitted along the entire length of the nerve fiber. Loss of myelin results in one or all of the following:

- conduction block at the site of lesion
- slower conduction time along the affected nerve
- increased subjective feeling of fatigue secondary to compensation for neurologic deficits

The primary triggers of inflammation result in auto-reactive cells being made. Then, the disease can go into a quiescent phase until secondary triggers come about. Blood-brain barrier permeability increases after secondary triggers have acted [12]. Then, there is amplification of the immune response, which goes into the inflammatory phase of the disease. If the inflammatory phase of the disease has not halted after several relapses and phases, it goes into a degenerative phase. With demyelination, there is also axonal loss with scarring, probably the most significant factor in disability.

There is evidence of blood-brain barrier disruption in the inflammatory stage of the disease. With peripheral initiation of disease and the secondary triggers coming in, activation and disruption of blood-brain barrier occur. The immune cells upregulate cell adhesion molecules of the blood-brain barrier, expediting cell entry and ingress of activated lymphocyte trafficking.

The blood-brain barrier consists of specialized endothelial cells with tight junctions. It is under the control of several adhesion cell molecules that allow trafficking of certain cells and controls, even solute trafficking of most substances. The process of lymphocyte trafficking through the blood-brain barrier involves lymphocytes first rolling around the endothelial membrane. They get arrested, usually with upregulation of the alpha-4, beta-1 integrin molecule or VCAM interactions with its ligand, and then firm adhesion involves other adhesion molecules. The transmigration follows from that. If this process is upregulated, it results in the increased trafficking of lymphocytes [12].

Microglial cell activation and demyelination is probably the key event that takes place in the final destruction of myelin. Proinflammatory cytokines activate the microglial cells, these release free oxygen, free radicals, and proteases that actually eat up the myelin, and cause the actual myelin loss. If unchecked, it almost always leads to axonal loss, and that's what ultimately causes irreversible damage in MS [13].

## 2.3 Causes

The predominant theory today is that MS results from attacks by an individual's immune system on the nervous system and it is therefore usually categorized as an autoimmune disease [14]. There is a minority view that MS is not an autoimmune disease, but rather a metabolically dependent

neurodegenerative disease. Although much is known about how MS causes damage, its exact cause remains unknown [15].

In MS, immune dysfunction can be detected locally in the central nervous system (CNS) and cerebral spinal fluid, as well as systemically in peripheral circulation. Autoimmune nature of MS has long been suspected. It is known that patients with MS have inflammation and demyelination in their CNS and oligoclonal bands in their cerebrospinal fluid. These abnormal immunoglobulins are identified in a high percentage of patients with clinically definite MS during exacerbations of relapsing-remitting disease, or persistently in significant proportion of chronic-progressive patients. A dysregulated immune system no longer prevents memory T-cells from becoming activated against myelin, entering the CNS, and mediating damage associated with the disease.

## 2.4 Treatments

There is no curative treatment available for MS [16]. However, a number of medications can be used to treat the disease symptomatically [17]. Corticosteroids are medications of choice for treating exacerbations. Interferon $\beta$ -1B (Betaseron.) as well as Interferon $\beta$ -1a (Avonex.) are successfully used to reduce the frequency and severity of relapses [18]. Interferon beta-1b (Betaseron) and interferon beta-1a (Avonex, Rebif) are genetically engineered copies of proteins that occur naturally in the body. They help fight viral infection and regulate the immune system [19].

Glatiramer (Copaxone) is an alternative to beta interferons for relapsing remitting MS. Doctors believe that glatiramer works by blocking the immune system's attack on myelin.

Natalizumab (Tysabri) is administered intravenously once a month. It works by blocking the attachment of immune cells to brain blood vessels — a necessary step for immune cells to cross into the brain — thus reducing the immune cells' inflammatory action on brain nerve cells [20]. Copolymer 1 is now being investigated in clinical trials and also appears to decrease the disease activity. Specific medications are also available to treat fatigue, pain, spasticity, bladder control problems, etc.

All of the above approaches address MS symptoms only (not causes), have side effects ranging from moderate to severe [21], and eventually lose their

impact. They are ‘magic bullet’ types of approaches, and, at a minimum, need to be supplemented by the anti-MS lifestyle that will be implied by our findings.

### 3. Approach

Figure 2 in Chapter 2 (also see [5]) is a flow chart that outlines the steps used in the present study. For the MS study, more steps from the flow chart were used than in the previous medical ODS LRD studies. This resulted in a very minor decrement in the streamlining of the process, and allowed for the retrieval of more potential discovery. The specific steps employed were as follows.

#### 3.1 Core MS Literature

The MEDLINE database was used, since we wanted to take advantage of the time-saving capabilities afforded by its MeSH taxonomy. The first step involved retrieving the core MS literature. We used the phrase “Multiple Sclerosis” (both as a MeSH term and a text phrase) as a query to retrieve the core MS literature (Steps 1 and 2 in Figure 2 of Chapter 2). Over the time period 1980-2007, we retrieved 28637 records total, of which 22864 records had Abstracts and could be used for clustering (June 2007).

#### 3.2. Directly Related Literature

In our three previous medical studies (RP, cataracts, PD), we used document clustering only to identify the main medical thrusts for query development. In the present MS study, we decided to supplement this document clustering step with other grouping approaches to ascertain what advantages, if any, the additional grouping approaches offer. We added auto-correlation mapping of phrases, and factor matrix analysis of phrases, using our TechOasis software package [22].

##### 3.2.1. Document Clustering

With use of our CLUTO document clustering software [23], which groups only those records that contain Abstracts, we grouped the 22864 retrieved records (MS core literature) into the main medical categories that characterize the MS core literature. These main medical thrusts (emphasizing biomedical phenomena) included: Demyelination and



remyelination; indirect auto-immune contributors to inflammation/ blood-brain-barrier; direct auto-immune contributors to inflammation; myelin basic protein, and viruses, as well as a number of diagnostic, treatment, symptom, genetic, and risk factor clusters (not included in query development).

### 3.2.2. Autocorrelation Maps and Factor Matrix Analysis

The phrase autocorrelation maps display phrases by their degree of correlation with each other, essentially based on their co-occurrence in Abstracts. Typically, a number of thematic phrase groups can be discerned from the map. The number of groups is used to estimate the number of factors required by the algorithm for factor matrix generation.

The factor matrix is a graphical representation of a factor analysis [24]. The columns are the factors, and represent important technical themes in the database. The rows are important technical phrases (selected by the analyst from all available phrases), and the numerical cell entries represent the quantitative contribution of a specific phrase to the theme of a specific factor.

Perhaps five-six groups could be distinguished from the autocorrelation map. The factor matrix analysis was then performed parametrically, with number of factors ranging from two to six. For the six factor matrix, the factor themes, and key (high value) phrases, were as follows:

Factor 1: Myelin sheath proteins and maintenance cells  
(myelin basic protein; myelin oligodendrocyte glycoprotein\*; proteolipid protein\*; experimental autoimmune encephalomyelitis; oligodendrocyte\*; encephalitogenic; epitope\*; immunization; immunodominant)

Factor 2: Indirect contribution of lymphocytes to inflammation by secretion of cytokines, chemokines, and lymphokines  
(cytokine\*; tumor necrosis factor-alpha; peripheral blood mononuclear cells; interferon-gamma ; proinflammatory; interleukin\*)

Factor 3: Viral contributions to inflammation  
(murine encephalomyelitis virus; virus ; viral; demyelinating)

Factor 4: Auto-immunity

(cerebrospinal fluid ; oligoclonal IgG bands;; isoelectric focusing; glial fibrillary acidic protein; Intrathecal IgG; IgG index; immunofixation; electrophoresis)

Factor 5: Demyelination and remyelination

(oligodendrocyte\*; demyelinat\*; glial fibrillary acidic protein; astrocyte\*; axon\*; myelin oligodendrocyte glycoprotein\* ; remyelinat\*)

Factor 6: Blood-brain-barrier

(vascular cell adhesion molecule-1; intercellular adhesion; ICAM-1; endothelial; endothelial cell\*; cell adhesion molecule; endothelium)

There is essentially a mapping between the clusters (from the document clustering analysis) and the six factors, with the exception that one of the clusters combines the indirect contribution of the lymphocytes to inflammation (secretion of cytokines, etc) with blood-brain-barrier disruption phenomena (endothelial cells/ vascular cell adhesion molecules), whereas the factor matrix treats these as two separate factors.

### 3.2.3. Directly Related Literature Query Development

The factors and clusters identified could be classified into two generic types. One type covers observable symptoms/characteristics of MS (demyelination, blood-brain-barrier disruption, to some extent), while the other type covers underlying causes (autoimmunity, viruses, inflammation). Test literature retrievals showed that the underlying phenomena retrievals (because of their generality, and applicability to many diseases) were an order of magnitude greater than the symptom-oriented retrievals (because of their relative specificity). In our previous ODS LRD medical studies (Chapters 3-5), the directly related literature queries tended to focus on the more specific characteristics of the disease, and the indirectly related literature queries tended to focus on the more generic underlying characteristics of the disease. We decided to follow the same strategy for the MS directly related literature query and indirectly related literature query. Thus, ‘directly related’ should be interpreted as the literature characteristic of the more specific/unique disease biomedical characteristics, and ‘indirectly related’ should be interpreted as the literature characteristic of the more generic disease biomedical characteristics.

In MS, the more specific/unique disease biomedical characteristics are the stripping of the myelin sheath from the axons, the loss of axons, and the death of the oligodendrocytes primarily, and the disruption and breakdown of the blood-brain barrier secondarily. These are not independent phenomena. We used the key phrases from the two clusters that addressed these directly related phenomena. We did not use combinatorials of these phrases in the directly related literature query, since the phrases are relatively specific, and combination of specific phrases would have been overly restrictive. We have found from the cataracts [2] and PD [3] studies that combinations of the more generic terms are extremely valuable for semantic filtering purposes, but combinations of specific terms may be excessively restrictive.

For analytical purposes (not discovery), we also wanted to retrieve core literature records in semantic classes of interest, those classes from which potential discovery could be drawn in the related literatures. Following our assumptions for potential solution classes made in our previous medical ODS LRD studies, we restricted potential discoveries from the related literatures to non-drug and lifestyle modification approaches. We then retrieved core MS records restricted to those classes where the non-drug class filter was approximated by (PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR FLAVONOIDS OR "DIETARY SUPPLEMENTS").

There were two classes of records in this ‘filtered’ retrieved core literature. One class of records, had they been in one of the related literatures, would have been potential discovery candidates. The other class, had they been in one of the related literatures, would not have been potential discovery candidates. We observed that the records in the first class, those most relevant to potential discovery, tended to have more than one of the key query mechanism terms (identified from the clusters) in the MeSH and text fields. We examined a sample of these records, and identified additional text and MeSH phrases from specific text and MeSH phrase patterns.

The key text terms identified through the CLUTO clustering process were: OLIGODENDROCYTE\*; REMYELINAT\*; AXON\*; DEMYELINAT\*; MYELIN BASIC PROTEIN\*; NORMAL WHITE MATTER; AXONAL DAMAGE; OLIGODENDROCYTE PROGENITOR CELLS;

MICROGLIA; MYELIN OLIGODENDROCYTE GLYCOPROTEIN;  
OPTIC NEURITIS; WHITE MATTER LESIONS;

The key text terms identified through examination of the interesting non-discovery records were: INFLAMMATORY AND (CYTOKINE\* OR MEDIATOR\*); OXIDATIVE PHOSPHORYLATION;  
MITOCHONDRIAL DYSFUNCTION; ATAXIA; DEMYELINAT\* OR DEMYELINATISATION; NEURODEGENERAT\*; OXIDATIVE STRESS; ANTIOXIDANT; CORPUS CALLOSUM; REMYELINAT\*; MYELIN REGENERATION; NEUROLOGIC DISABILITY;  
OLIGODENDROCYTE\* AND (APOPTOSIS OR DEATH OR DEGENERATION OR DAMAGE OR DYSTROPHY);  
NEUROINFLAMMAT\*; NEUROPROTECTION; MICROGLIA\*;  
MITOCHONDRIAL INSUFFICIENCY; REACTIVE OXYGEN SPECIES;  
AXONAL AND (DEMYELINATION OR DESTRUCTION); RADICAL SCAVENGING; MUSCLE SPASTICITY; MYELIN\* AND (FORMATION OR DAMAGE OR REGENERATION OR PHAGOCYTOSIS); INHIBIT\* AND (COMPLEMENT OR CYTOKINE\*);  
OLIGODENDROGLIAL APTOSIS; OPTIC NEURITIS;  
AUTOREACTIVE T-CELLS; PHOSPHATE DEPLETION; OXIDATIVE REACTIONS.

The key MeSH terms identified through the CLUTO clustering process were: MUSCLE SPASTICITY; ATAXIA; NERVE DEGENERATION;  
TNF-RELATED APOPTOSIS; COGNITIVE DISORDERS;  
NEUROGENIC INFLAMMATION; ANTIOXIDANTS;  
NEURODEGENERATIVE DISEASES; OXIDATIVE STRESS;  
NERVOUS SYSTEM DISEASES; DEMYELINATING DISEASECORPUS CALLOSUM; COGNITION DISORDERS; MYELIN SHEATH;  
REGENERATION; OLIGODENDROGLIA.

The key MeSH terms identified through examination of the interesting non-discovery records were: MYELIN BASIC PROTEINS; NERVE REGENERATION; AXONS; MYELIN ASSOCIATED GLYCOPROTEINS; CELL DEATH; NERVE GROWTH FACTOR;  
MITOCHONDRIAL DISEASES; TREMOR; REACTIVE OXYGEN SPECIES; APOPTOSIS REGULATORY PROTEINS;  
NEUROPROTECTIVE AGENTS; DEMYELINATING AUTOIMMUNE DISEASES; ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL;

COMPLEMENT INACTIVATOR PROTEINS; OPTIC NEURITIS; ANTI-INFLAMMATORY AGENTS; MICROGLIA; HYPOPHOSPHATEMIA.

Using all the text and MeSH phrases obtained from the clustering, factor matrix analysis, phrase auto-correlation map, and identification of text patterns in interesting core non-discovery records (restricted to the two primary medical thrusts mentioned above), we generated a query for retrieving the directly related literature unrestricted to semantic classes. This query was as follows:

((demyelinat\* OR remyelinat\* OR "myelin sheath pathology" OR ("myelin sheath" AND (damage OR degenerat\*)) OR "axonal loss" OR "axonal destruction" OR (oligodendrocyte\* AND (apoptosis OR death OR degenerat\* OR damage OR dystrophy)) OR (oligodendroglia\* AND (apoptosis OR destruct\* OR loss))) OR ("blood-brain barrier" AND (disruption OR "cell adhesion" OR "activated lymphocyte\*" OR "adhesion molecule\*" OR (lymphocyte\* AND trafficking) OR breakdown OR transmigration OR dissolution)))) NOT "multiple sclerosis"

The first group of terms represents the biomedical phenomena that comprise the main thrusts of the MS core literature (essentially degradation of the myelin sheath and disruption/breakdown of the blood-brain barrier), and the final negation term '(Multiple Sclerosis)' insures that the records retrieved will be disjoint from the core MS literature. The terms were used to search the text fields and the MeSH field, and 25504 semantically-unrestricted records were retrieved.

The query was then intersected with the same semantic classes identified for core literature analysis, the resultant terms were used to search the text fields and the MeSH field, and 427 semantically-restricted records were retrieved.

Some examples of potential discovery from these 427 directly related literature retrievals are listed in the Results section.

### 3.3. Indirectly Related Literature

To obtain potential discovery from the indirectly related literature, the following steps were taken. The directly related literature (the fraction of the 25504 records mentioned above with Abstracts) was clustered using CLUTO, and the main medical thrusts were identified from the text phrases

in each cluster's Abstracts and the MeSH terms. Additionally, phrase autocorrelation maps and factor matrices were generated.

In parallel, as in the development of the directly related literature query, the potential discovery candidate records from the directly related literature were examined for textual patterns both in the Abstract text and in the MeSH terms especially compared to textual patterns from the non-discovery records. We observed that the non-discovery records typically contained one of the key phrases as a MeSH term (sometimes none) and as a text term as well, whereas the potential discovery candidates typically contained *two or more* of the key phrases as MeSH terms (and as text terms as well).

All the above input data were integrated, and a query was generated. There were three main components to the query: biomedical, negation, semantic classes. The biomedical component consisted of five sub-components, based on biomedical thrusts. The terms for the five biomedical sub-components (thrusts) are as follows:

#### Thrust 1 - Myelin Dysfunction

- 1 = (Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR Death))
- 2 = ("Schwann Cell Cytoplasm" OR "Schwann Cell Proliferation" OR "Schwann Cell Differentiation")
- 3 = ("Microglial Cell\*" OR "microglial Activation" OR "microglial Death")
- 4 = ("Mitochondrial Dysfunction" OR "mitochondrial Swelling")
- 5 = "Mitogen-Activated Protein Kinase Kinases"
- 6 = "Mitogen-Activated Protein Kinases"
- 7 = "Glial Fibrillary Acidic Protein"
- 8 = (Astrocyte\* AND Reactiv\*)
- 9 = "Oxidative Phosphorylation"
- 10 = (Caspase-3 AND Activat\*)
- 11 = "Nerve Degeneration"
- 12 = "Enzyme Activation"
- 13 = "Enzyme Inhibitors"

#### Thrust 2 – Oxidation Destruction

- 1= "Neurodegenerative Disease\*"
- 2= "Reactive Oxygen Species"

- 3= "Oxidation-Reduction"
- 4= "Hydrogen Peroxide"
- 5= "Oxidative Stress"
- 6= "Free Radicals"
- 7= Antioxidants

#### Thrust 3 – Blood-Brain Barrier Disruption

- 1= "Cell Membrane Permeability"
- 2= "Active Biological Transport"
- 3= "Endothelial Growth Factor\*"
- 4= "Cell Surface receptors"
- 5= "Capillary Permeability"
- 6= "Blood-Brain Barrier"
- 7= "Carrier Protein\*"
- 8= "Tight Junction\*"

#### Thrust 4 – Myelin Inflammation

- 1= "Tumor Necrosis Factor receptor\*"
- 2= "recombinant Interferon Gamma"
- 3= "Inflammatory Response"
- 4= "Inflammatory Cytokine\*"
- 5= "Activated Macrophage\*"
- 6= "Macrophage Infiltration"
- 7= "Interferon Type II"

#### Thrust 5 – Autoimmune Myelin Destruction

- 1= ("Myelin Basic Protein\*" AND Immunology)
- 2= ("Peptide Fragment\*" AND Immunology)
- 3= "Major Histocompatibility Complex"
- 4= "CD4 Positive T-Lymphocyte\*"
- 5= "CD8 Positive T-Lymphocyte\*"
- 6= (Antigens AND Immunology)
- 7= "Blood Mononuclear Cell\*"
- 8= "Leukocyte Chemotaxis"
- 9= "Immunophenotyping"

Each biomedical sub-component contained a combinatorial grouping of the terms within the sub-component only (intra-thrust combinations). For the first two sub-components listed above, which contained relatively generic terms, all combinations of three terms were used combinatorially in the query. For the last three sub-components listed above, which contained more relatively specific terms, all combinations of two terms were used combinatorially in the query. The full query is contained in Appendix 3 of this monograph.

In some sense, *the biomedical phenomena combinations component can be viewed as a filter that targets potential discovery candidates more precisely, based on patterns associated with previously-identified potential discoveries*. Whether this combination approach also filters out potential discovery remains to be seen. For the present study, this was not an issue, since we obtained large amounts of potential discovery.

The second of the query components was the negation component (the core MS query and the directly related literature query, connected to the biomedical component by the NOT Boolean to insure that the indirectly related literature would be disjoint from the core and directly related literatures). This two component unrestricted indirectly related literature query returned 38190 records.

The third query component (semantic class restriction) was then added to the query to retrieve the filtered indirectly related literature records. A sampling showed there was a reasonable fraction of potential discovery candidates. Use of additional medical thrust text or MeSH phrases would have returned additional records and additional potential discovery candidates. Some examples of potential discovery from the indirectly related literature retrieved by this query are shown in the Results section. The vetting issues are similar to those from the PD study, and are discussed in [3].

#### 4. Results

This section contains representative examples of potential discovery from literatures related directly and indirectly to the core MS literature. Before proceeding to analyses, we present a few illustrative examples from the core MS literature restricted to semantic classes. While these are not discovery, they nevertheless reflect the types of impact that the non-drug approaches could potentially have for delaying or preventing the onset of MS. In



addition, as we will discuss later, some of these core concepts are prime candidates for innovation.

For example, UCP4-mRNA expression is increased in brain cells of rats maintained on caloric restriction. Neural cells with increased levels of UCP4 exhibit reduced reactive oxygen species (ROS) production and decreased mitochondrial calcium accumulation. The UCP4-mediated shift in energy metabolism reduces ROS production and increases the resistance of neurons to oxidative and mitochondrial stress, providing antiaging and neuroprotective effects [25]. Side effects of caloric restriction, as exhibited in rodent and primate studies, are positive on many fronts, and include increased life span [26]. There is an accumulating body of evidence for the positive effects of caloric restriction on UCP4 and other coupling proteins in both the MS core and none-core literatures, yet we have seen no mention of this harmless supplement in any of the mainline reviews.

#### 4.1. Non-Drug Concepts in the Core MS Literature

1. “***Prenatal hypovitaminosis D*** causes a dramatic dysregulation of several biological pathways including oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, chaperoning, post-translational modifications, synaptic plasticity and neurotransmission. A computational analysis of these data suggests that impaired synaptic network may be a consequence of mitochondrial dysfunction. Since disruptions of mitochondrial metabolism have been associated with both multiple sclerosis and schizophrenia, developmental vitamin D deficiency may be a heuristic animal model for the study of these two brain diseases.” [27]

2. “Synthetic metal ion chelators continue to show promise as a new therapeutic approach for neurodegenerative disorders. ***Dietary chelators***, unlike most vitamins, are, however, capable of negating or even reversing the roles of metal ions by: (i) decorporation of metal ions, (ii) redox silencing, (iii) dissolution of deposits, and (iv) generation of an antioxidant enzyme mimetic. This review gives a critical evaluation of recent progress in, and potential for, dietary control of neurodegeneration on the basis of the formation of antioxidant enzyme mimetics.” [28]

3. “....we have experimented with ***alternate day calorie restriction***, one day consuming 20-50% of estimated daily caloric requirement and the next day ad lib eating, and have observed health benefits starting in as little as two

weeks, in insulin resistance, asthma, seasonal allergies, infectious diseases of viral, bacterial and fungal origin (viral URI, recurrent bacterial tonsillitis, chronic sinusitis, periodontal disease), autoimmune disorder (rheumatoid arthritis), osteoarthritis, symptoms due to CNS inflammatory lesions (Tourette's, Meniere's) cardiac arrhythmias (PVCs, atrial fibrillation), menopause related hot flashes. We hypothesize that other many conditions would be delayed, prevented or improved, including Alzheimer's, Parkinson's, multiple sclerosis, brain injury due to thrombotic stroke atherosclerosis, NIDDM, congestive heart failure.” [29]

4. The positive preclinical outcomes in treating CNS disorders by complement regulatory molecules, such as vaccinia virus complement control protein, suggest the possibility of using **complement-inhibitory molecules** as neuroprotective agents. Several active ingredients of herbal origin are found to have complement-inhibitory activity. These herbal ingredients along with other anti-inflammatory roles might be useful in treating neuroinflammation associated with CNS disorders. Active ingredients of herbal origin with complement inhibitory ingredients are summarized and classified according to their chemical nature and specificity towards the major pathways activating the complement system. The structure activity relationship of some specific examples is also discussed in this report. This information might be helpful in formulating a natural panacea against complement-mediated neuroinflammation. [30]

5. “**N. sativa** may protect brain and medulla spinalis tissues against oxidative stress induced by EAE. In addition, N. sativa display its antioxidant and regulatory effects via inflammatory cells rather than the host tissue (brain and medulla spinalis) for EAE in rats”. [31]

6. “Recent studies in multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis (EAE), point to the fact that even in the early phase of inflammation, neuronal pathology plays a pivotal role in the sustained disability of affected individuals. We show that the major green tea constituent, **(-)-epigallocatechin-3-gallate (EGCG)**, dramatically suppresses EAE induced by proteolipid protein 139-151. EGCG reduced clinical severity when given at initiation or after the onset of EAE by both limiting brain inflammation and reducing neuronal damage”. [32]

7. , we show that in vivo treatment of SJL/J mice with **quercetin** (i.p. 50 or 100 microg every other day) ameliorates EAE in association with the

inhibition of IL-12 production and neural antigen-specific Th1 differentiation. .... suggest its use in the treatment of MS and other Th1 cell-mediated autoimmune diseases.” [33]

#### 4.1.1 Observations on non-drug core MS Literature concepts

When reviewing the large number of interesting core MS literature concepts, it became clear that a number were in common with those from the PD literature (including concepts from both literatures not reported in this paper or the PD paper). The question arose whether this commonality extended to other neurodegenerative diseases as well (we did not address commonality beyond neurodegenerative diseases, although, as was shown by the sulforaphane example in the PD study [3], there may well be commonality of interesting concepts (potential treatments) among neurodegenerative and non-neurodegenerative ailments). A brief study was undertaken comparing potential treatments in the core literatures of MS, PD, AD (Alzheimer’s Disease), and HD (Huntington Disease), and searching for those that are common.

For each of these diseases, the core literature was retrieved, and intersected with the non-drug semantic classes (as was done in the MS study reported here). Initially, the MeSH terms from each literature were extracted, tagged, and combined. Later, the same process was applied to the Abstract text phrases. Those common to four diseases, common to three diseases, two diseases, and those applied to one disease only, were identified.

The MeSH terms common to four and three diseases were inspected visually, and those reflecting potential treatments were extracted. Only a handful existed for MeSH terms common to four diseases. One reason was that the core HD literature was much smaller than the other three core literatures (almost by an order of magnitude), and limited the number of concepts available. Many more potential treatments were common among three diseases, mainly (not exclusively) those with the larger core literatures.

For the MeSH terms, potential core treatments common among four diseases included: ***Caloric Restriction, Tea (Green Tea), Smoking Elimination, Omega-3 Fatty Acids, Exercise.*** ***Potential core treatments common among three diseases included: Ginko Biloba, Curcumin, Blueberry, Quercetin, Mercury Elimination.***

For the Abstract phrases, potential core treatments common among four diseases included: ***Zinc and Smoking Habits***, and biomedical phenomena common among four diseases included ***Mitochondrial Dysfunction, Oxidative Stress, and Tardive Dyskinesia***. ***Potential core treatments common among three diseases included: Alcohol Consumption (reduce), Ascorbic Acid, Beta-Carotene, Cannabinoids, Curcumin, Dairy Products (reduce), Green Tea, Fruit, Ginko Biloba, etc***.

The universality of some of these potential treatments must be treated with caution. Clinical medicine is replete with treatment strategies that are effective in one organ system or for one class of disease that (by our understanding of pathophysiology) should also be useful in other organs and/or disease classes, yet when tested, they are ineffective.

Finally, for those readers interested in a more comprehensive overview of the contents of the non-drug core neurodegenerative disease literature in MEDLINE, see Appendices 7-11. We used a moderately more comprehensive list of semantic classes than we had used for the PD or MS studies, and present the citations for the retrieval listed in Appendices 7-11. Specifically, these appendices contain retrievals for AD, PD, MS, ALS, HD, respectively, arranged in order of number of articles with Abstracts. No analyses were performed on these records in Appendices 7-11; because of their modest numbers, they can be perused visually quite rapidly. In Appendix 6, we performed a clustering analysis of a PD non-drug core retrieval with an even more expanded list of semantic classes, and presented results for each cluster in the hierarchical taxonomy.

#### 4.2. Non-Drug Potential Discovery Concepts in the Directly Related Literature

“On the basis of these results, ***PA [petasignolide A]*** is suggested to be a major neuroprotective agent primarily responsible for the protective action of the butanol fraction of *P. japonicus* extract against kainic acid-induced neurotoxicity in the brains of mice.” [34].

“These results suggest that orally administered ***QF808 [Mangifera indica L. extract]*** is absorbed across the blood-brain barrier and attenuates neuronal death of the hippocampal CA1 area after ischaemia-reperfusion. These protective effects are most likely due to the antioxidant activity of QF808.” [35].

“...**tiliroside and gnaphaliin** are antioxidants against in vitro Cu(2+)-induced LDL oxidation in the same order of magnitude compared to that of the reference drug, probucol.” [36].

“Tissue damage was slowed by decreased levels of glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) and an associated rise in lipid peroxidation (LPO) in mitochondria, which were reversed by **CQE [Cissus quadrangularis extract]**. In addition, CQE prevents oxidative damage of DNA by reducing DNA fragmentation indicating its block on cell death. Ulcer protection in CQE treated rats was confirmed by histoarchitecture, which was comprised of reduced size of ulcer crater and restoration of mucosal epithelium. Thus, reduced neutrophil infiltration, antiapoptotic and antioxidant action have a pivotal role in the gastroprotective effect of CQE.” [37].

“**AIAE [Artemisia iwayomogi]** attenuated the phorbol 12-myristate 13-acetate plus calcium ionophore A23187-stimulated tumor necrosis factor-alpha and interleukin-6 secretion in human mast cells.” [38]

#### 4.3. Non-Drug Potential Discovery Concepts in the Indirectly Related Literature

**Kalpaamruthaa (KA)** showed an enhanced antioxidant potential in the management of a rheumatoid arthritis model in rats. "Kalpaamruthaa (KA), a modified indigenous Siddha preparation constituting Semecarpus anacardium nut milk extract (SA), Emblica officinalis (EO) and honey was evaluated for its synergistic antioxidant potential in adjuvant induced arthritic rats than sole SA treatment....The profound antioxidant efficacy of KA than SA alone might be due to the synergistic action of the polyphenols such as flavonoids, tannins and other compounds such as vitamin C and hydroxycinnamates present in KA." [39]  
(Another example of the benefits of synergistic combinations)

**Salvia miltiorrhiza Bunge** (a Chinese herbal medicine) attenuates increased endothelial permeability induced by TNF-alpha. "Salvia miltiorrhiza Bunge, a traditional Chinese herbal medicine, is often used for prevention and treatment of cardiovascular disorders such as atherosclerosis.... Data from this study suggest that one of the mechanisms S. miltiorrhiza exerts its pharmacological effect is through

its modulation of endothelial cell permeability." [40]

**Inchinko TJ-135** (a Japanese herbal medicine) inhibits inflammatory cytokines and enhances production of anti-inflammatory cytokines. "These results suggest that con A-induced hepatitis was ameliorated by pretreatment with TJ-135. With regard to the mechanism of these effects of TJ-135, we speculate that TJ-135 inhibits the production of inflammatory cytokine and enhances the production of anti-inflammatory cytokines. Therefore administration of TJ-135 may be useful in patients with severe acute hepatitis accompanying cholestasis or in those with autoimmune hepatitis." [41].

"These results suggest that **SM [Silymarin]** may to protect the SNC [substantia nigra pars compacta] by oxidative damage for its ability to prevent lipid peroxidation and replenishing the GSH levels." [42]

"Potent free radical scavenger, **edaravone**, suppresses oxidative stress-induced endothelial damage". [43]

"**Sopoongsan** inhibits mast cell-mediated anaphylactic reactions and inflammatory cytokine secretion." [44]

"**Rhapontigenin**, isolated from the Korean medicinal plant **Rheum undulatum**, was found to scavenge intracellular reactive oxygen species and hydrogen peroxide. Rhapontigenin protected against oxidative stress-induced cellular damage such as H<sub>2</sub>O<sub>2</sub>-induced membrane lipid peroxidation and cellular DNA damage. Rhapontigenin protected cells against oxidative damage by enhancing cellular antioxidant activity and modulating cellular signal pathways" [45].

**Butea monosperma lam.**, a methanol extract of Butea monosperma flowers, was found by the Pharmacy Department of the University of Baroda in India to be an antioxidant. Free radical scavenging activities was demonstrated against 2,2 diphenyl-1-picrylhydrazyl (DPPH) radical, nitric oxide radical, superoxide anion radical, hydroxyl radical, and 2, 2' azo-bis (amidinopropane) dihydrochloride (AAPH) [46].

Because the purpose of the MS study was to demonstrate an approach, and not necessarily to be comprehensive, a number of shortcuts were taken. Not all possible semantic categories for potential discoveries were identified,

only the most obvious. Relatively few terms were selected for both the direct and indirect queries; many more were available. Not all retrieved records were examined; only enough to demonstrate the quality of results. The potential expansion to indirectly related literatures using citation linking described previously was not done. Thus, the results obtained should be viewed as the tip of a very large iceberg.

#### 4.5. Discussion

The picture from the handful of potential discoveries reported in this paper (and the hundreds of additional potential discoveries possible with a properly resourced study) is a synergy of lifestyle/ dietary practices that could be interpreted as ***anti-MS***. Along with non-discovery items such as Vitamin D, dietary chelators, caloric restriction, complement-inhibitory herbs, Nigella Sativa Oil, green tea, and quercetin are potential discovery items such as Shogaol, Ethanol, Iron, Petaslinolide A, Mangifera Indica L, Tiliroside, Gnaphaliin, Cissus Quadrangularis Extract, Kalpaamruthaa, Salvia Miltiorrhiza Bunge, Inchinko TJ-135, Silymarin, Edaravone, Sopoongsan, and Artemesia Iwayomogi. As stated above, more laboratory tests and field trials would have to be done on all these items to insure that they are anti-MS and safe, but these preliminary literature-based results offer some promise of what is possible.

We are finding a major disconnect between the therapies presently or potentially available presented on all the major medical Web sites (and in MS mainstream journal review papers), and the therapies suggested by what has already been demonstrated in the core MS literature, much less what we have generated from the related literatures. The major medical Web sites (and journal reviews) present about a half-dozen drug treatment options for MS. We have seen very few medical Web sites that even mention any of the non-drug approaches shown in the MS core results section. We believe the core literature and related literature potential discoveries and innovations have the potential to supplement the mainline medical treatments.

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## **Chapter 7 - LITERATURE-RELATED DISCOVERY: WATER PURIFICATION**

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### **1.1. Purpose of Study**

We, and the rest of the ODS LRD community, have been using ODS LRD to identify potential treatments or preventative actions for challenging medical problems, among myriad other applications. The previous four chapters in this monograph describe the application of ODS LRD (specifically, the ODS LBD variant) to RP (Chapter 3; also see [1]), cataracts (Chapter 4; also see [2]), PD (Chapter 5; also see [3]), and MS (Chapter 6; also see [4]).

The goal of the present study was to determine whether LRD could be successfully applied (for the first time) to a challenging non-medical problem to generate potential discovery. Additionally, we wanted to explore the use of both LRD variants (LBD and LAD) to a non-medical problem.

The extremely positive results from the RP study spawned a larger study on WP. We selected the specific problem of WP because of universal applicability and sponsor interest. Its objectives were to identify potential improvements in the water purification process, especially (but not limited to) cost reduction. Two LBD approaches were selected: cluster filtering and latent semantic indexing (LSI). One LAD approach was selected: Broad Agency Announcement Notification.

Cluster filtering was inspired by the use of cluster analysis in query development. When we clustered retrievals of mixed relevant and non-relevant records to some topical query, we noticed that the clustering tended to segregate the relevant from the non-relevant records. As stated in the first author's patent: "Document clustering tends to group documents into groups that are at similar levels of relevance. A technical expert then samples documents from each group, and performs a final judgment as to the relevance of each group." [5]. The reason for this segregation was that the relevant records would contain a number of terms related to the query topic, whereas the non-relevant records would typically contain one query term. In the article's context, the term tended to be peripheral to the theme of the query. The non-relevant records would form into clusters each of which

centered about the one query term, and the relevant records would multi-link cluster around the multiple terms. We hypothesized that this relevant/non-relevant segregation could be extrapolated to searching for discovery. However, the remainder of the cluster filtering approach was conceptually similar to that used in the RP study, and was manually intensive.

LSI-based discovery was an attempt to use more sophisticated algorithms to help identify potential discovery candidates. It allowed much easier access to very remotely related literatures compared to the manually intensive methods described above.

Even though the cluster filtering approach started chronologically much later than the LSI approach, the cluster filtering approach will be described first. It is more closely related to the RP approach than is the LSI approach. The LAD approach will be summarized briefly at the end.

## 1.2. LBD Approaches and Results

### 1.2.1. CLUSTER FILTERING

#### 1.2.1.1 Background of Water Purification

Water purification is the process of removing contaminants from a raw water source. The goal is to produce water for a specific purpose with a treatment profile designed to limit the inclusion of specific materials; most water is purified for human consumption drinking water. Water purification may remove large particulates such as sand; suspended particles of organic material such as parasites, Giardia, Cryptosporidium, bacteria, algae, virus, fungi; minerals such as calcium, silica, magnesium; and toxic metals such as lead, copper and chrome. Some purification may be elective in its inclusion in the purification process, such as remedies for smell (hydrogen sulfide remediation), taste (mineral extraction), and appearance (iron encapsulation) [6]). There are many ways to purify water, and most are based on the size of the contaminants involved.

The major areas of water treatment and the prevalent technologies that are associated with them are listed below.

- Particle Filtration - coagulation/flocculation/clarification, multi-media filtration (anthracite, sand, garnet), continuous micro-filtration

- Organics Removal - carbon filtration, UV, ozone
- Water Softening - ion exchange, chemical precipitation
- De-ionization - reverse osmosis, ion exchange, electro de-ionization
- Particle removal - ultrafiltration, nanofiltration

Some ancillary areas of water purification include:

- Disinfection - chloramines, chlorine dioxide, ozone
- Corrosion control
- Biofouling control

A typical water purification plant operates using six main steps: pre-treatment, pH adjustment, coagulation and flocculation, sedimentation, filtration, and disinfection. [6].

#### (1) Pre-treatment

The first step in purifying surface water is to remove large debris such as sticks, leaves, trash and other large particles which may interfere with subsequent purification steps.

#### (2) pH adjustment

Distilled water has an average pH of 7 (neither alkaline nor acidic) and sea water has an average pH of 8.3 (slightly alkaline). If the water is acidic (lower than 7), lime or soda ash is added to raise the pH.

#### (3) Coagulation and Flocculation

Together, coagulation and flocculation are clarification methods that work by using chemicals which effectively "glue" small suspended particles together, so that they settle out of the water or stick to sand or other granules in a granular media filter.

#### (4) Sedimentation

Water exiting the flocculation basin may enter the sedimentation basin, also called a clarifier or settling basin. It is a large tank with slow flow, allowing floc to settle to the bottom.

#### (5) Filtration

After separating most floc, the water is filtered as the final step to remove remaining suspended particles and unsettled floc. The most common type of filter is a rapid sand filter.

#### (6) Disinfection

Disinfection is normally the last step in purifying drinking water. Water is disinfected to kill any pathogens which pass through the filters.

### 1.2.1.2 Approach

Because this was the first LBD study of a non-medical technical topic that reported potential discovery, a number of heuristic approaches were tested. They all had the following common features.

#### 1.2.1.2.1 Retrieve Core Literature

The first step was to generate a query for retrieving the core WP literature. For very specific core topics (e.g. membrane fouling), terms were used for a query that would retrieve a literature focused on the topic of interest. For membrane fouling, the records retrieved would be viewed as pertaining to membrane fouling by experts in the field. Then, a phrase frequency and proximity analysis of the retrieved records was performed.

#### 1.2.1.2.2 Retrieve Expanded Literature

Phrases and phrase combinations were selected that generalized the fundamental mechanisms represented by the core literature. In the membrane fouling case, terms such as foul\* or antifoul\* were selected. Use of these terms in a query would retrieve the core membrane fouling records, but would also retrieve fouling records that had little relation to membrane fouling (e.g. fouling of marine sponges) other than they both were based on the surface fouling mechanism. The core literature records were subtracted



from the total generic query retrieval, and the remaining records were called the “expanded” literature.

For less focused core topics (e.g. water purification), an iterative approach was used to define a more comprehensive core literature [7]. The core literature was then clustered, the main technical themes identified, and phrases characteristic of each main theme were generalized as in the fouling example above. Thus, ‘water purification’ might be generalized to ‘purification,’ all ‘purification’ records retrieved, and phrases that contained some variant of purify\* that were based on some sort of separation mechanism were selected for the query [8]. This allowed records to be retrieved from literatures such as protein purification or DNA purification.

Since there were many phrases in the core water purification literature that could be generalized, some general phrase selection criteria were necessary. Documents such as Sandia’s Water Purification Roadmap [9] or the National Academy of Sciences Review of the Roadmap were examined [10], and some of the critical technologies identified in these expert-based documents were included in the query as phrases to be generalized.

#### 1.2.1.2.3 Identifying Potential Discovery

Irrespective of how the expanded literature was defined, the following method was used to identify potential discovery. A document clustering algorithm [11] was used to group the expanded records by similarity into cohesive categories. The category themes were examined; some of the categories contained multiple members that represent starting points for potential discoveries, whereas other categories contained none. Those that had unique features with discovery potential were examined in detail and individual discoveries were identified.

Another way the clustering methodology was used was to examine the expanded literature clusters and specific abstracts to identify *areas* of potential discovery for further investigation. The areas could be either specific or general, but general, more diverse areas are better for the clustering methodology than are small highly focused areas. (An example of a general area would be the “filters” or “barriers” literature, and a more highly focused area would be “filter-feeders.”) These phrases of interest were selected from both individual abstracts and from a specific cluster’s phrase frequency information, or overall theme. These phrases were entered

into the Science Citation Index (SCI) [12] search engine on an individual phrase basis and were then downloaded and put into the clustering algorithm. At this point, the clusters were systematically searched for unique (highly unconventional, disparate from core literature) areas that could contain discovery. Some potential discoveries were fully vetted, and are shown in the results section.

### 1.2.1.3 Results Obtained Using the Cluster-based LRD Methodology

#### 1.2.1.3.1 Sample Query Terms

Table 1 shows examples of core query terms and expanded query terms. Note the specificity of the core terms and the generality of the expanded terms.

**Table 1 - Core and expanded core query terms.**

| <b><u>Core Query</u></b> | <b><u>Expanded Query</u></b> |
|--------------------------|------------------------------|
| water treatment          | vacuum extraction            |
| water recycling          | separation mechanism         |
| water purification       | transport selectivity        |
| wastewater treatment     | phase extraction             |
| treated water            | oxygen mass transfer         |
| reverse osmosis          | selective adsorption         |
| desalination             | fouling resistance           |
|                          | centrifugation               |
|                          | air purification             |

#### 1.2.1.3.2 Potential Discovery Examples

Below we provide some potential discovery records; format is Abstract excerpt followed by the reference and rationale linking the concept to water purification. These have been vetted via the procedure discussed in [13].

1. "...plasmin specifically hydrolyzes proteins participating in cell adhesion (fibronectin, vitronectin, and laminin) and does not affect nonadhesive proteins..." [14]

Plasmin or some derivative thereof with respect to proteins that allow cells to attach could be used to create anti-fouling coatings for use on/in filter membranes in water purification systems

2. "It is shown how the complex, 'composite anatomical structure' of roots results in a 'composite transport' of both water and solutes. Parallel apoplastic, symplastic and transcellular pathways play an important role during the passage of water across the different tissues. These are arranged in series within the root cylinder (epidermis, exodermis, central cortex, endodermis, pericycle stelar parenchyma, and tracheary elements)... there is a rapid exchange of water between parallel radial pathways because, in contrast to solutes such as nutrient ions, water permeates cell membranes readily. The roles of apoplastic barriers (Casparian bands and suberin lamellae) in the root's endo-and exodermis are discussed. The model allows for special characteristics of roots such as a high hydraulic conductivity (water permeability) in the presence of a low permeability of nutrient ions once taken up into the stele by active processes... " [15].

Biomimetic membranes based on plant root physiology could be used as efficient water purification methodologies.

3. "The effects of surface magnetism, using perpendicularly polarized magnetic media, are evaluated on *Bacillus licheniformis*.... At different spin directions we are able to observe a change on the biofilm formation, protein synthesis, and cell growth rate. Given that surface energy can easily penetrate through cells, this approach is an advantage over existing techniques that require direct physical contact to target cells. It also presents a new technique to cell adhesion and synthesis of surface proteins." [16]

Magnetic fields or magnetically charged membranes could be used to deter fouling of water purification membranes or other important components in water purification systems.

4. "Fresh-water atyid shrimps are an ancient group of carideans that uses "passive" cleaning mechanisms to protect their gills from fouling... Gill cleaning in atyids involves epipod-setobranch complexes, associated with their pereopods, and multidenticulate setae on the posterior end of the scaphognathite.." [17]

The passive cleaning mechanisms of the atyid shrimp could be reproduced and used to clean and/or prevent the fouling of filters and membranes in water purification systems.

5. "Recently, non-leaching, permanent, sterile-surface materials have been developed in which one end of a long-chained hydrophobic polycation containing antimicrobial monomers is attached covalently to the surface of a material, for example, cotton or plastic. The polymeric chain allows the antimicrobial moieties to permeate into, and kill, the cells of the pathogen. These sterile-surface materials kill both air- and waterborne pathogens and are not susceptible to existing resistance mechanisms." [18]

Previously, sterile surface materials have been considered to prevent surface infections in medical-based applications. Our discovery in this case is the fact that the specific sterile surface materials discussed in this abstract may be incorporated into water purification membranes to deter or eliminate fouling

6. "Despite their high nutritional value and a lack of physical defenses, most marine sponges appear to be minimally affected by predators, competitors, and fouling organisms, possibly due to sponge chemical defenses.... Formoside and other triterpene glycosides from *Erylus formosus* deterred predation, microbial attachment, and fouling by invertebrates and algae." [19]

Compounds (triterpene glycoside) could be used to create anti-fouling coatings or materials (perhaps non-leaching) for use on/in filter membranes in water purification systems

#### 1.2.1.4 Future Studies

Compared to the medical topic queries, the water purification queries were more complex. This was due in part to the absence of a MeSH taxonomy equivalent in the SCI. It was also due to the broader scope of the indirectly related literature relating to all the many facets of water purification technology. In the SCI, many words/phrases were required to cover a category, whereas in MEDLINE, a MeSH term could perform the same function.

Future non-medical topic studies could be based on the same generic core-directly related-indirectly related expansion process used for the medical topic. The clustering selection process for potential discovery would be used on both the directly indirectly related expansion literatures. While the clustering procedure of visual inspection is manually intensive, the clustering does offer time savings relative to the visual inspection procedure used for the RP study, and it also allows for groups of potential discoveries to be located in addition to specific individual discoveries.

Also in future studies, once groups/items have been identified in the expanded literature by the clustering methodologies listed in the previous section, the SCI itself can be queried to produce individual discoveries if the keywords taken from the Abstracts or individual clusters are specific enough. This method is useful for searching focused areas of much larger scientific areas, such as the filtration of water in the kidney literature, or filter feeding animals in the “filter” literature. Two examples from each of these areas are listed below.

1. " The kidneys filter the plasma in special filtration units-glomeruli-and thereby excrete low-molecular-weight waste products into the urine. The mechanisms of glomerular filtration have been a matter of controversy for several decades, but recent data have revealed new details about the molecular nature of the filter and have demonstrated a central role for the podocyte slit diaphragm in the filtration process. " [20].

The functionality of the kidney, and specifically its glomular filtration capability along with the mechanics of its ability to separate fluids (with the use of its slit diaphragms, fenestrated endothelium, glomerular basement membrane (GBM), and epithelial filtration slits) may be used to create new membranes for use in water purification membranes.

2. " The article is devoted to individual behaviour of autozooids (mainly connected with feeding and cleaning) in 40 species and subspecies of marine bryozoans from the White Sea and the Barents Sea. We present comparative descriptions of the observations and for the first time describe some of autozooidal activities (e.g. cleaning of the colony surface by a reversal of tentacular ciliature beating, variants of testing-position, and particle capture and rejection)." [21]

Using the same cleaning processes that autozooids employ, namely the movement of the cilia, it may be possible to create self cleaning filters, or self cleaning membranes.

#### 1.2.2.1 LSI FILTERING

Latent Semantic Indexing (LSI) is a special case of Latent Feature Indexing (LFI, proposed by the first author). One of the earliest references to the general application of LSI to objects and descriptors can be found in Berry's paper [22]. In LSI, a standard term by document matrix  $D$  can be shown to be equivalent to the product of three other matrices, obtained through the process of singular value decomposition factoring. In effect, terms and documents are represented in the same  $m$ -dimensional space (where  $m$  is the number of linearly independent rows, and columns, in  $D$ ). The value of this representation is that  $m$  can be reduced substantially to some value  $k$  to give an optimal reduced dimensional approximation of  $D$ . In practice, this allows two documents that use strongly overlapping vocabulary to be retrieved even if a particular query only uses the terms that index one of them.

In LFI, use of any feature is allowable, not only Abstract words or phrases. If Authors are substituted for Words/ Phrases, then the mathematical operations are the same for reduced dimensional approximation of  $D$  (by least squares criterion). The same will be true for Institutions, although the utility of using Authors or Institutions does not seem particularly high, from our present perspective. Probably the most useful feature (other than Words/Phrases) will be Latent Citation Indexing, where Citations are substituted for Words/ Phrases. This would allow concepts related due to their use of common references to be accessed, allowing for the possibility of similar concepts with very dis-similar terminology due to a terminology-standardizing query not having been introduced into the process. The reader is referred to [23] for an overview of the use of citation analysis for several application areas including clustering and authority identification particularly with regards to webpages.

#### 1.2.2.2 Document Preprocessing.

We were initially provided a set of documents that had been produced via a Simulated Nucleation process [7]. This set of documents contained both core documents, directly related to water purification, and expanded core documents that would serve as the source of potential discoveries related to

the water purification problem. One of the first steps in the LSI-based discovery process was dividing the documents into a set of core documents and a set of expanded core documents.

We first identified the core documents by tagging those documents as core if they matched a focused core water purification query. Some of the terms that were included in this query include “water purification OR water treatment OR water recycling OR water disinfection OR water desalination.” Documents that matched this query were marked as core documents and the remaining documents were marked as expanded core documents.

After the documents were divided into a set of core and expanded core documents, the document collections were subjected to standard stop word removal and stemming procedures. The document collection was stemmed using our own implementation of the Porter stemmer [24]. Stop word removal was accomplished using a standard list of stop words although our software, literature-based discovery (LBD) 1.0, provides the user with the capability to remove frequent or infrequent words. Each document was encoded using a standard vector space encoding after stemming and stop word removal. Our software allows the user to utilize standard term frequency inverse document frequency (TFIDF) [25] and mutual information (MI) [26] based vector normalization schemes. TFIDF weighting was used by default in these simulations.

After the documents were encoded using a vector space scheme, duplicate documents were removed. Documents were marked as duplicates if the cosine of the angle between the vector space encoding of the documents exceeded a threshold  $\tau$ . Various values were tried for  $\tau$  with an ultimate value of .90 being used in this study. At this point in time, one now has a term document matrix where each column in the matrix represents a document and each document has been labeled as a core document or an expanded core document.

### **1.2.2.3 The LSI Procedure.**

The use of singular value decomposition as an alternative to conventional keyword indexing was first proposed by Deerwester [27]. This approach, known as latent semantic indexing (LSI) or latent semantic analysis (LSA), reduces the noise in the term-document matrix while providing a

semantically relevant projection of documents and terms. A term is a single word that appears in the corpus after stop word removal and stemming. In keeping with the original implementation of LSI, our LRD procedure currently uses terms as defined above, i.e. single word phrases. Future versions of our tool will incorporate the use of single and double word phrases into the LRD process. Let  $\mathbf{X}$  be the  $t \times d$  matrix representing the  $t$  terms in  $d$  documents. Using singular value decomposition, we can write

$$\mathbf{X} = \mathbf{T}_0 \mathbf{S}_0 \mathbf{D}_0',$$

where  $\mathbf{T}_0$  is the matrix of left singular vectors,  $\mathbf{S}_0$  is the diagonal matrix of singular values, and  $\mathbf{D}_0$  is the matrix of right singular vectors. The diagonal elements of  $\mathbf{S}_0$  are all positive and can be assumed (without loss of generality) to be ordered in decreasing magnitude. Since the vectors in  $\mathbf{T}_0$  span the columns of  $\mathbf{X}$ , they span the document space. Similarly, since the vectors in  $\mathbf{D}_0$  span the rows of  $\mathbf{X}$ , they span the term space. These provide us with a convenient mechanism to render the documents and the terms within the same space.

A rank  $k$  approximation of the original matrix  $\mathbf{X}$  is obtained by taking the top  $k$  singular values

$$\hat{\mathbf{X}} = \mathbf{T} \mathbf{S} \mathbf{D}',$$

where  $\mathbf{T}$  is  $t \times k$ ,  $\mathbf{S}$  is  $k \times k$ , and  $\mathbf{D}'$  is  $k \times d$ .  $\hat{\mathbf{X}}$  is the closest rank  $k$  approximation to  $\mathbf{X}$  in a least squares sense. By choosing  $k$  to be much smaller than the full rank of the matrix  $\mathbf{X}$ , the projection will simultaneously reduce the noise in the document collection and also ensure that semantically-related documents will be located near each other in the projected space. In the case of supervised learning applications,  $k$  can be chosen in order to maximize probability of correct classification.

In the current LSI-based LBD approach,  $k$  is chosen as follows: if the number of documents is less than 3000,  $k$  is set to be 10% of the number of documents; if the number of documents is greater than or equal to 3000,  $k$  is set to be 300. The use of  $k=300$  for large document collections is a recommended size based on previous LSI studies in document retrieval [28, 29]. The use of 10% of the document size for document collections less than 3000 was based on the fact that as the number of documents shrinks one would expect the ambient semantic space also shrinks. The number of dimensions at the boundary between the two  $k$  selection methodologies is identical at 300 and then it shrinks in a linear manner taking on a value of



200 at 2000, 100 at 1000 etc. The choice of  $k$  in text retrieval applications is a hotly debated topic, and more research is required to develop better selection rules for  $k$ . It is expected that smaller values of  $k$  would lead to more radical discovery but would also result in a larger number of more spurious associations. This is the probability of detection vs. probability of false alarm type of tradeoff that is usually encountered in statistical pattern recognition applications.

The projection of the data serves the purpose of preserving and emphasizing semantic relationships among documents. In any dimensionality reduction technique, once the projection of the data to a lower dimensional space is performed, one can compute the dissimilarity in the reduced rank space. The hope is that the dissimilarities in the reduced rank space give more faithful representations of the relationships among the data.

Gordon and Dumais [30] first suggested applying LSI to the LBD process. Their fundamental idea was that one could look for associations among the terms in the document collection via the use of the reduced rank  $D$  matrix to project the document terms into a common space. The reader is reminded that the discovery process can be viewed as a search to link a set of core articles (concepts or terms)  $C$  to a set of intermediary expanded core articles (concepts or terms)  $B$  and ultimately to a set of expanded core articles (concepts or terms)  $A$  that contain a potential solution to the problem of interest. This is usually represented as a  $C \rightarrow B \rightarrow A$  connection. Gordon and Dumais suggested that one could look for the  $C \rightarrow B$  associations,  $B \rightarrow A$  associations or even directly identify the  $C \rightarrow A$  associations in the projection space obtained using the reduced rank matrix  $D$ .

Our approach extends that of Gordon and Dumais in several ways. In their original paper, they alluded to the fact that one could identify associations between articles rather than concepts. However, they did not employ this as part of their LSI-based LBD procedure. Our software implementation allows a user to query for, and have returned a set of, core articles, based on LSI-obtained indexing using the reduced rank matrix  $T$ . It then identifies those expanded core articles that are part of the nearest neighbor structure of the original core articles. In this way, one can identify potential discoveries via the identification of core to expanded core article relationships in the LSI projected space.

#### **1.2.2.4 Use of the Minimal Spanning Tree**

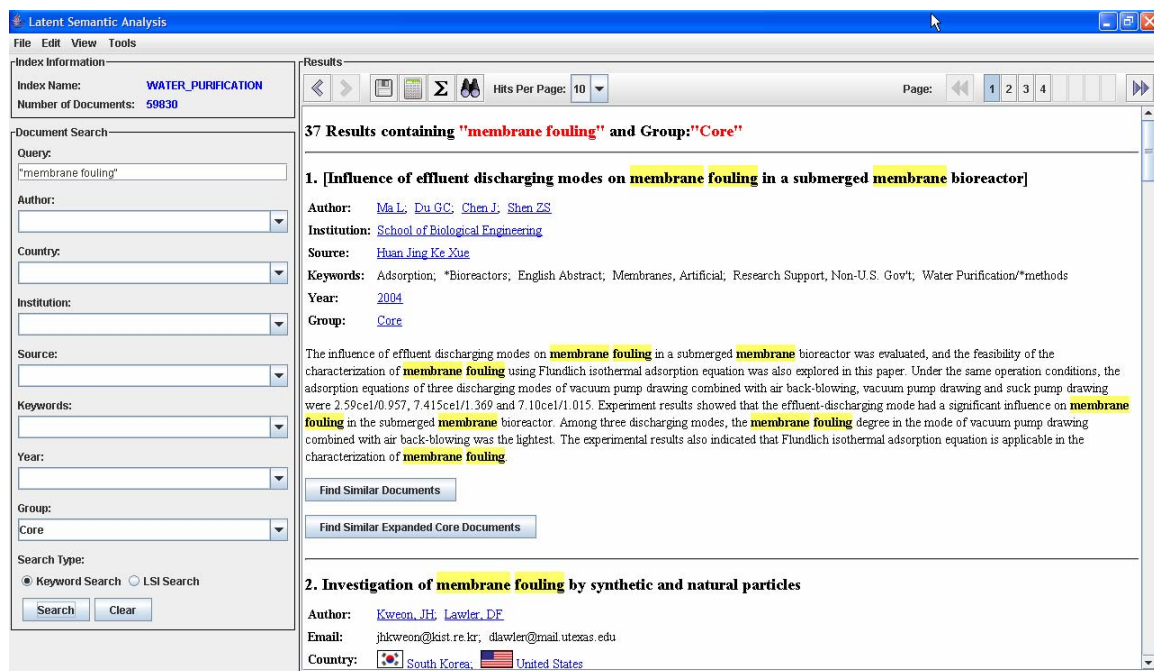
The second extension on the original work of Gordon and Dumais utilizes a minimal spanning tree (MST) as a means to investigate the set of core to expanded core term relationships in the LSI-obtained term space. We had previously suggested the use of MSTs in order to identify interesting article associations between disparate corpora [31]. Our reason for the introduction of the MST into our current procedure was as follows. The original Gordon and Dumais approach merely provided the user with a list of LSI sorted potential discovery terms with no way to ascertain the semantic relationship between the terms. In this manner, the user might be forced to investigate the discovery potential of several terms that were closely related to one another and hence duplicitous in terms of their discovery potential. The MST calculated on the discovery term to discovery term associations is one method to provide this type of feedback to the user since duplicitous terms are likely to be close to one another in the calculated MST. The hope is that in this way the user would have more time to make additional discovery, since they do not have to investigate these duplications. The second benefit of the MST is that the user can start at a potential discovery term and then identify terms that are nearby, several links away, in the MST that may be new discoveries. This is an advantage over merely providing the user with a sorted list of terms based on LSI score. This would allow the user to make additional discoveries by being able to investigate terms that are semantically related to given discovery terms although the terms might be quite further down the LSI sorted list. The increased discoveries based on the easy identification of duplicate discovery terms in conjunction with the easy identification of potential new discovery terms would be best quantified via a study on the original RP data. Such a study will have to be the subject of our future investigations. For now, our claim is that users of our software how found the MST useful for both of these functions.

Within the venue of the current work, one first computes the interpoint distance matrix between the various terms in the article collection in the LSI-projected space. The interpoint distance matrix is obtained using 1 minus the cosine similarity measure of the terms. Viewing the collection of terms as a graph, one node per each term, this interpoint distance matrix can be used to determine a complete graph between the terms. A complete graph

is one in which there is an edge between each pair of nodes, One can then compute a MST on this complete graph. A MST serves as a simpler less complicated graph that encompasses the information contained in the complete graph. A traversal through the MST provides an ordering of the terms that is equivalent to a divisive clustering of the term interpoint distance matrix under a complete distance metric. In fact, making a sequence of longest length cuts on the MST is equivalent to a divisive clustering of the term interpoint distance matrix. Therefore, the ordering of the nodes (terms) in this case would be the order that would come out of such a clustering. This MST-based space and its associated ordering allow the user to more quickly explore the set of possible core to expanded core term relationships within the document collection because it provides a contextually meaningful arrangement of the terms.

### 1.2.2.5 The Software Framework

Figure 1 contains a screen snapshot of the results of a query for “membrane fouling” within the core article collection.

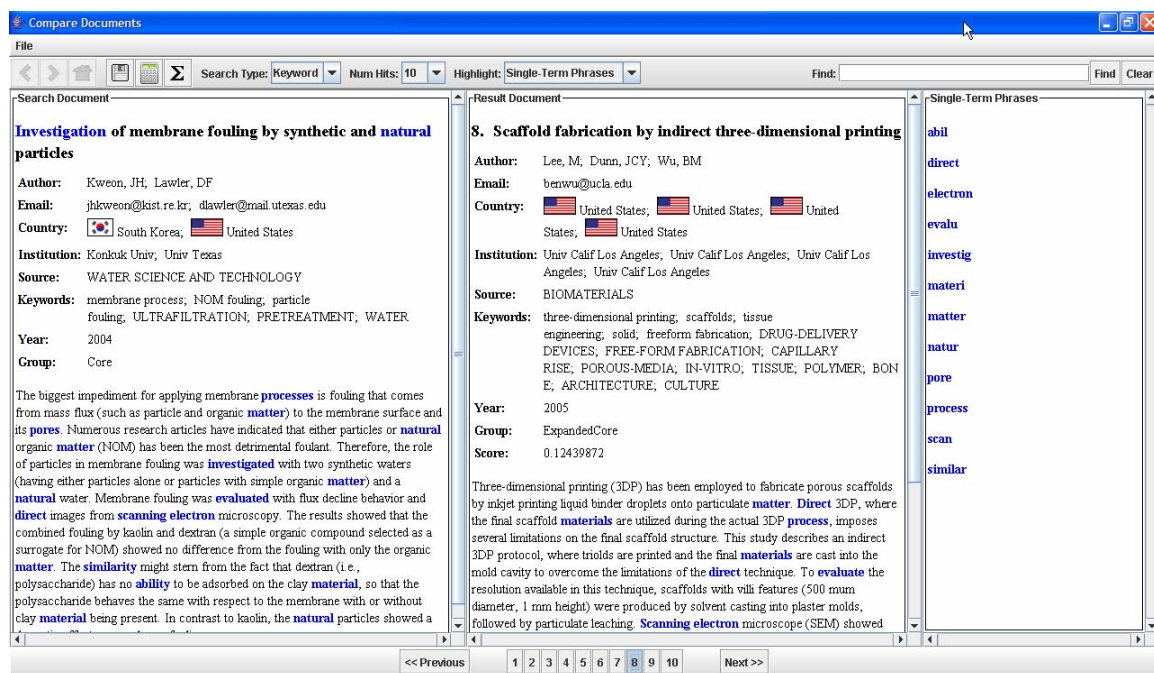


**Figure 1 - Results of the query "membrane fouling" within the core document collection.**

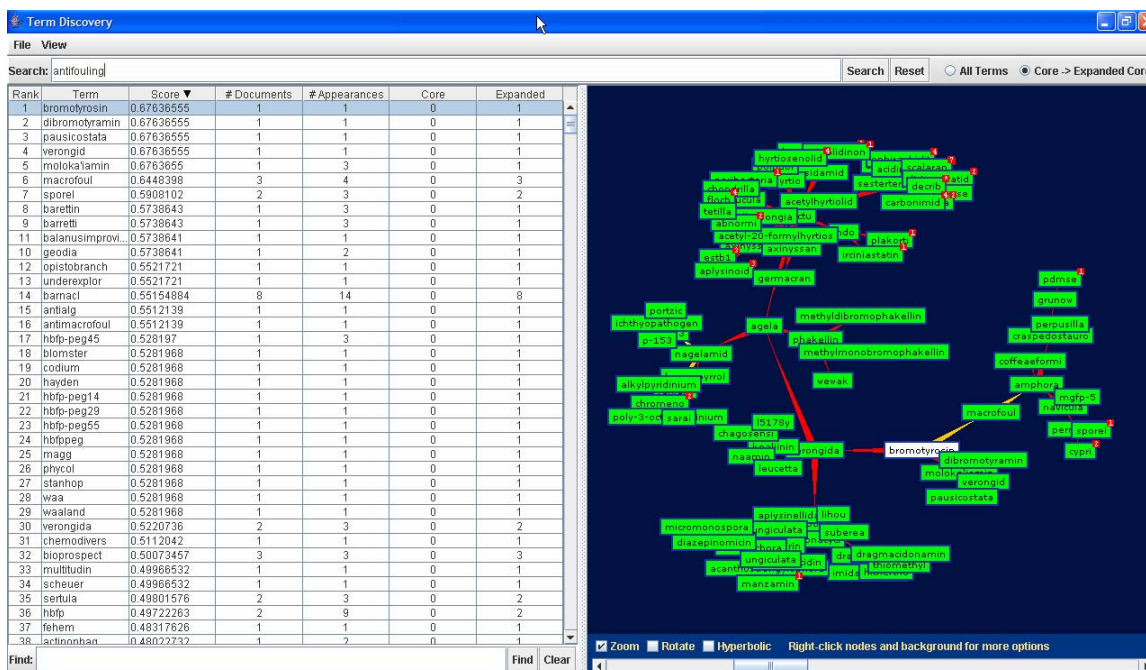
This initial query within the core literature was performed using keyword indexing in order to find those core documents with the phrase “membrane

fouling.” As shown in Figure 1, 37 articles were retrieved, and two articles are displayed (the second one partially). The second article returned details the effect of synthetic and natural particulate matter on membrane fouling. We will select this core article as the starting point, and use the LSI capability to locate similar expanded core documents. This is the manner in which one can use the tool to identify potential discoveries in the expanded core articles related to specific core articles.

In Figure 2, we illustrate a core article and its associated expanded core article in LSI space. The core article was the second one shown on Figure 1. The relationship between the core and expanded core article is as follows. The expanded core article is within the LSI calculated nearest neighbor structure of the core article. The core article discusses membrane fouling by natural and synthetic processes. One of the factors in this type of effect is the nature of the pores in the membrane and the relationship between the fouling agents and these pores. The expanded core article discusses the use of a three dimensional printing technique for the production of biological materials. Pores are also discussed in this Abstract. Use of these scaffolds as created via three-dimensional printing might offer up an alternative fabrication methodology to create water purification membranes.



**Figure 2 – The relationship between a core and expanded core article in LSI space. The expanded core article presents a potential discovery.**



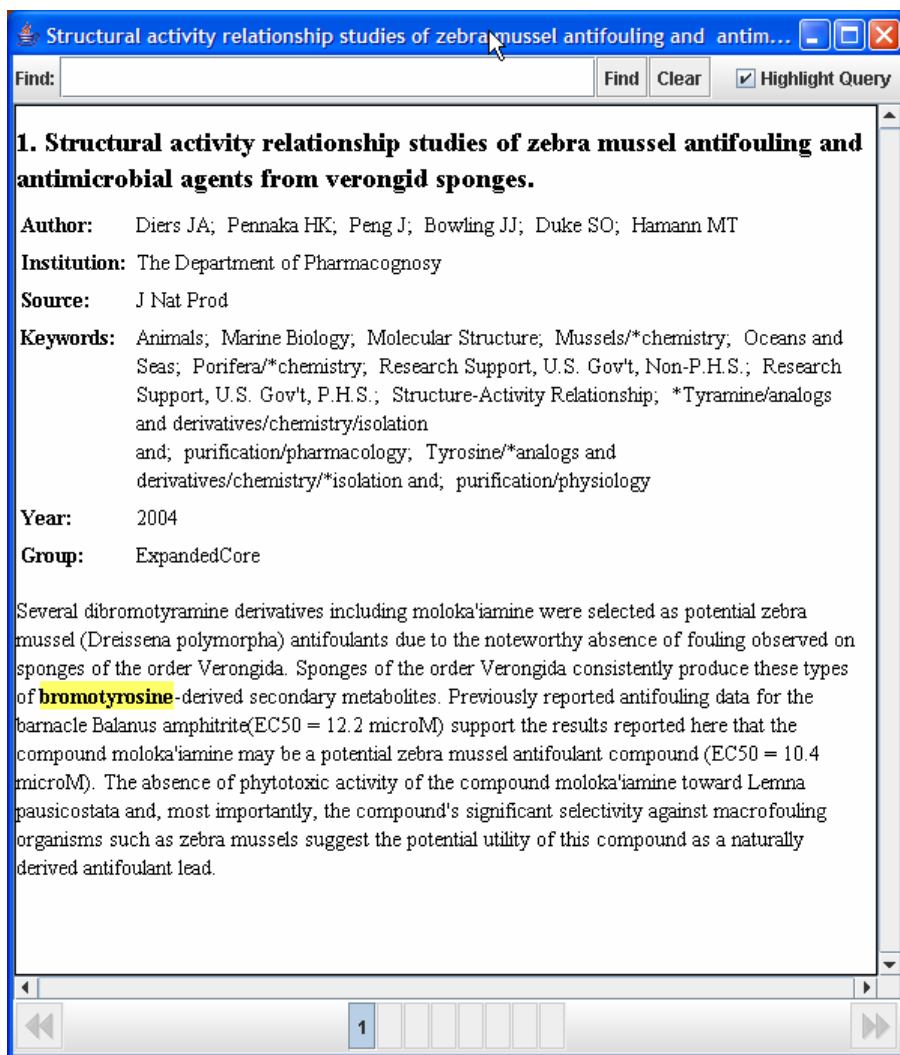
**Figure 3 - A screen snapshot of the term to term discovery tool.**

Figure 3 provides a screen snapshot of the term discovery tool. In this case we have entered the term “antifouling.” The tool allows us to look for all of the terms that are near this term, or just the expanded core terms that are near this term, in LSI space. In this case, we have chosen to look just for expanded core terms that are near the term ‘antifouling’. The leftmost window lists the terms as sorted by cosine similarity score in the LSI projected space along with the total number of appearances of the term, the number of documents in which the term appears, and the number of core and expanded core documents in which the term appears. The users can choose to sort by any of the columns that they deem appropriate. We point out that each of the terms does not appear in any of the core documents. This is in keeping with the radio button that was clicked in the user window of the software which controls this behavior.

The rightmost window displays a folded version of the minimal spanning tree as computed on the cosine similarity obtained interpoint distance matrix in the LSI projected term space. Our current software lists the top 1000 nodes and this tree display would become much too busy without folding a portion of the tree in order to hide its presence from the user. The white box in the tree is the term that has the current focus in both windows. In this case

the term is “bromotyrosine.” Several of the terms that are near this term in the MST have similar “similarity to antifouling” scores and these come from the same article. For example one can see “dibromotyramin” a stemming of “dibromotyramine.”

The tool provides the user with the capability to drill down, from either window, in order to identify those articles that contain this particular term. Figure 4 displays the results of drilling down to list the articles that contain the term “bromotyrosine.” This article discusses the fact that veongid sponges have the capability to generate compounds for self protection that are antifouling and antimicrobial in nature. One of the vetted discoveries discussed in the cluster-based LBD section was related to sponges and one of the potential discoveries that will be discussed in the discovery portion of this section is related to sponges. This Abstract represents another potential discovery of sponge-based compounds although the compounds mentioned in this particular abstract have not currently been vetted. The fact that there may be a plethora of discoveries related to the sponge family is appropriate given their somewhat tenuous position in the sea-based food chain.



**Figure 4 - A listing of the expanded core article containing the term bromotyrosine.**

### 1.2.2.6 Example Potential Discoveries Obtained Using the LSI-based LBD Procedure.

A few potential discoveries (obtained using the LSI-based discovery methodology) are listed below. These discoveries run the gamut from strategies to defeat membrane fouling to ideas for biological agent deactivation within water and even include an idea with regards to a new desalination methodology based on eel physiology. We believe that this list of potential discoveries represents the tip of the iceberg in terms of number of discoveries that are possible using this strategy.

1 - “Previous studies have shown that high molecular weight non-dialysable material (**NDNI derived from cranberry juice**) inhibits the adhesion of *Escherichia coli* and the coaggregation of a variety of oral bacteria [32, 33].

High molecular weight non-dialysable materials derived from cranberry juice can be used to prevent membrane fouling in water purification membranes. Specifically, discrete flavonoids called condensed tannins, or proanthocyanidins (PACs) have previously documented anti-adhesion properties.

2 – “In this work, we show the potent antifouling effects of two compounds, **barettin (cyclo[(6-bromo-8-entryptophan)arginine]) (1), isolated as a Z/E mixture (87/13), and 8,9-dihydrobarettin (cyclo[(6-bromotryptophan)arginine]) (2)**, isolated from the marine sponge *Geodia barrette* [34].

Brominated cyclopeptides or their derivatives may offer a means of preventing membrane fouling in water purification membranes. The effects of the compounds responsible for the sponges’ antifouling mechanism are reversible and nontoxic.

3 – “In the present study, we investigated the antibacterial and antifungal effects of **essential oils extracted from the coniferous species *Pinus densiflora*, *Pinus koraiensis*, and *Chamaecyparis obtusa***, because their biological activities have not been yet elucidated [35].



Coniferous essential oils might provide a means to deactivate microbes and fungi in water. The exact mechanism of the action of these essential oils is still being studied.

4 – “Complementary DNAs encoding homologs of the mammalian aquaglyceroporins (termed AQPe) and aquaporin-1 isoforms (termed AQP1) were isolated from the European eel. The AQP amino acid sequences share 35-54% identity with other known human AQPs. Although AQPe mRNA expression was approximately equivalent along the entire length of the gut, AQP1 expression was the highest in the posterior/rectal segment. **Seawater (SW) acclimation increased AQP1 mRNA abundance** ... [36]

Saltwater eels have adapted to life under conditions of extremely high salinity. Study of desalination methodologies employed by the eel along the length of its digestive track may allow for the development of radically new desalination methods.

5. “The vital barrier function of the skin resides primarily in the top stratum of the epidermis, the **stratum corneum** (SC). The SC is the barrier to the passive diffusion of water out of the skin, allowing us to live in air without suffering from dehydration, and is the barrier to other molecules including irritants into the skin [37].

Materials that mimic the barrier function of the skin and the stratum corneum could be created and used as new membranes for use in water purification systems. Specific studies of the properties of keratin might aid in the development of new membrane-based systems.

6. “**Filter feeding** in doliolids is re-described. Feeding involves the dorsal spiral volute of the peripharyngeal bands, which rotates the filter in the pharynx so that particles inhaled are trapped between two layers of the mucous filter.” [38]

A novel filter may be created for use in water purification systems that mimic the functionality of the filter feeding mechanisms of Doliolum. Nanotechnology-based approaches may offer an implementation strategy for such filters.

Table 2 provides a listing of the cluster-based discoveries and the LSI-based discoveries. Both techniques produce viable discoveries that stood up to inspection under the first three steps of our vetting process. Let's take a moment to compare the nature of the discoveries produced by these two procedures. First we note that the list of discoveries for each technique have a high percentage of biologically inspired discoveries, 4 of 6 in the case of the cluster-based methodology, and 6 of 6 in the case of the LSI-based methodology. Given that each of the two discovery procedures is somewhat exploratory in nature this fact represents more of a bias of the software users towards the investigation of those types of discoveries with the tool than any particular bias of the tool itself to find only biologically inspired discoveries. It is the case of course that several of the most recent exciting discoveries in recent years have been based on the inner working of biological systems , genetic algorithms for example. The clustering-based discoveries run the gamut from totally new mechanisms for filtration based on plant roots to several ideas for the defeat of membrane fouling including antifouling coatings based on glycosides, the use of magnetic fields to defeat fouling and shrimp-based self cleaning mechanisms. The LSI-based discoveries offer several new strategies for antifouling including the use of cranberry juice derivatives and brominated cyclopeptides. This method also produced discoveries for new self cleaning membranes based on filter feeders. We finally note that this method also produced a radically new idea for water filtration systems based on skin corneum and strategies for biological deactivation based on the user of coniferous essential oils.

These really represent the “tip of the iceberg” in terms to the potential discoveries that can be identified using our methodologies. The reader is referred to [39] for a full discussion of the discoveries obtained using these two methods and other methods that were developed during the course of our research but were not discussed here. The full characterization of the strengths and weaknesses of our two developed approaches will have to be relegated to future investigations.

**Table 2 - Comparison of the cluster-based discoveries and the lsi-based discoveries.**

| Clustering-based Discovery                     | LSI-based Discovery  |
|--|--|
| Plasmin based hydrolysis of adhesion proteins. | Cranberry juice extracts to prevent membrane fouling.  |
| Biometric material based on plant roots.       | Brominated cyclopeptides or other compound utilized by <i>Geodia barrette</i> could help prevent membrane fouling. |

|   |  |
|---|--|
| Use of magnetic fields to defeat membrane fouling.                              | Microbe and fungi deactivation in water using coniferous essential oils.                                       |
| Use of atyid shrimp gill cleaning mechanisms to design self-cleaning membranes. | Systems modeled on aquaporin-like systems based on eel gut physiology might offer a new means of desalination. |
| Sterile surface materials to eliminate or deter membrane fouling.               | New water purification membranes based on the skin and stratum corneum.  |
| Triterpene glycosides as antifouling membrane coatings.                         | Purification systems that mimics the functionality of the filter feeding mechanisms of Doliolum.               |

### 1.2.2.7 Conclusions

#### Cluster Filtering

The cluster-based methodology obtains candidate discovery terms via either a phrase frequency or cluster analysis of the expanded core. It then uses these discovery candidates to go back into the literature and obtain additional articles that are related to the particular discovery term but which might not have been downloaded as part of the initial topic area data collection, in this case water purification. These articles are then subjected to human inspection and additional analyses which could nullify the proposed discovery, strengthen it, or lead the user into a totally different discovery area.

#### LSI

We have demonstrated the application of an LSI based approach to LBD in order to discover new methods of water purification. Our proposed methodology allows one to make discoveries in two different ways. Both approaches start off with a core/expanded core document collection as obtained via the simulated nucleation procedure. In the first approach, one locates those expanded core articles that are near a collection of core articles in LSI space. It is expected that the original collection of these core articles of interest would be returned based on a keyword query into our existent core/expanded core dataset. We have use various techniques to determine the core query including terms obtained from reading the literature, terms based on a simple phrase frequency analysis of the core document collection, and terms as extracted as part of the clustering of the core literature. Once the collection of relevant core articles is returned the user

then explores the expanded core nearest neighbors for this core article collection.

In the second discovery approach, one locates expanded core terms that lie near a core term in LSI space. Once again, it is expected that the user provides an initial core term and, once again, these terms can be selected based on user intuition/interest, simple phrase frequency analysis of the core literature or phrases extracted as part of clustering the core literature. The user then explores the expanded core terms that are near this core term either using a sorted drop down list or using a MST-based interface. In either case, our proposed approaches allow a natural interaction between the LSI discovery process and phrase frequency analysis or cluster analysis.

### Cluster Filter/LSI Comparison

We will now take a moment to compare the two approaches. The LSI-based approaches initially use a phrase frequency analysis or clustering of the core articles as a starting point for the discovery process. The cluster-based approach uses a phrase frequency analysis or clustering of the expanded core articles as a starting point for the process. Both discovery methodologies are exploratory in nature in that a human user helps to decide what particular cluster or phrase is a good candidate for additional analysis. So in a real sense neither approach is fully automated. The other difference between the two methods is that the LSI-based method is a closed method which looks for discoveries on a pre-existing set of core/expanded core documents while the cluster-based approach is an open system that allows the user to bring additional documents into the discovery process.

One might imagine a hybrid system that incorporated both approaches. One could for example use the cluster-based approach to bring in a collection of new documents that represent potential discoveries and then render these in LSI space. One could then look for relationships between the original core documents and this new collection of expanded core documents. This could be at the core document to expanded core document level or at the core term to expanded core term level. The hope would be that this analysis might indicate to the human user another discovery that was not initially anticipated when the human user initially obtained the new set of potential discovery documents.

In addition, we have illustrated the use of a MST-based approach to the exploration of the core term to expanded core term discovery relationships. In future work, we plan to illustrate the application of the procedure to other non-medical problems, to attempt to quantify the benefits of the application of the MST-based approach to discovery term exploration, to investigate the relationship between choice of  $k$  in the LSI procedure and quality/quantity of the discoveries, and to attempt to quantify the difference in performance between the clustering based approach and the LSI based approach. We are particularly interested in the applicability of the approach to large datasets.

Finally, we have placed a more comprehensive list of potential discovery candidates in Appendix 12. They remain to be fully vetted.

### **1.3. LAD Approach and Results**

#### **1.3.1. WATER PURIFICATION**

##### **1.3.1.1. BAA NOTIFICATION**

A Broad Agency Announcement (BAA) is a continuously open announcement by a Federal funding agency intended to solicit research ideas for the purpose of investment. Even though BAAs are posted on widely accessible sites, Program Managers in charge of the BAA will usually send notice of the announcement to experts in the field of the BAA, to insure they are aware of the posting. There is no set number of recipients, but the distribution range is usually from a few tens to a few hundreds.

The objective of the BAA notification study was to insure that researchers from disciplines not normally associated with water purification would be aware of a water purification BAA. This could potentially result in proposals from disciplines not normally associated with water purification being submitted, with the higher potential for radical discovery.

##### **1.3.1.2. APPROACH**

The overall approach was to develop a core literature query for water purification, generalize the core literature query into an expanded literature query, retrieve the relevant core and expanded literature articles from appropriate databases, and insure that the authors of the articles received notice of the BAA Announcement. The same water purification core and

expanded literature queries that were used for the water purification LBD studies described earlier in this paper were used for the BAA Notification study.

The queries were entered into the Science Citation Index and the NSF Agency Awards database, and a few thousand articles were retrieved. Announcements were sent to the authors of these articles. About 300 pre-proposals were received as a result of the BAA posting, three times the number that were received a year earlier resulting from a similar water purification BAA.

### 1.3.1.3. RESULTS

Because of the sensitivities of the competitive and proposal evaluation process, no details related to the evaluation or eventual funding can be provided. However, we evaluated the relationship of each proposed concept to what is normally associated with water purification, and calculated an overall statistic for the received proposals. About 2/3 of the pre-proposals were judged to have originated in technical disciplines not normally associated with water purification. Many of these appeared to offer potential for real discovery.

The lessons learned from this experiment are discussed in the last paper in this Special Issue [40].

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## **Chapter 8 - LITERATURE-RELATED DISCOVERY: LESSONS LEARNED, AND FUTURE RESEARCH DIRECTIONS**

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### **1. INTRODUCTION**

Chapters 3-7 presented the specific approaches and results for five topical ODS LRD studies (also see [1]-[5]). This final chapter will integrate the findings and experiences from the five topical ODS LBD studies and the one topical ODS LAD study, address the lessons learned, and provide recommendations for future ODS LBD and ODS LAD research. The overarching lessons learned will be presented as the main text of the chapter. The specific lessons learned from the main discovery process steps will be presented in section 4 of this chapter.

### **2. LESSONS LEARNED – PRE/POST-DISCOVERY PROCESS**

#### **2a. Promise of Literature-Based Discovery**

The basic tenet of ODS literature-based discovery (LBD) is that:

- 1) there are a massive number of technical concepts in the total technical literature;
- 2) there are an extraordinary number of potential linkages among these concepts;
- 3) a fraction of the total number of linkages may result in useful potential discovery;
- 4) even a very small fraction of a massive number could result in a substantial number of potential discoveries worth pursuing.

Based on the substantial amount of potential discovery we have generated from our five topical demonstration studies (most of which were minimally resourced), and the massive amount of potential discovery we project based on adequately funded studies, we believe the basic tenet of ODS LBD is correct. There is much potential payoff from properly funded and conducted ODS LBD.

## 2b. Fundamental Assumptions in ODS LRD

There are at least three fundamental assumptions that have been used in whole or part by the ODS LRD research community [6], and these assumptions may be partly responsible for limiting the quantity and quality of potential discovery that has been reported. First, the foundational assumption is that true discovery is possible if two literatures with some intrinsic relationship are consciously linked for the first time. While this assumption is valid conceptually, it has strong limitations in practice.

It is based on the belief that researchers in areas directly related to the problem or topic of interest will be narrowly focused on their own discipline, and will be unaware of the potential relationship of their own research to the problem of interest. While there may be some researchers for whom this assumption will be valid, it certainly will not be true for all researchers. For a reasonable number of researchers working in disciplines related to the problem of interest, there will be a few who are quite aware of the potential relationships to the problem of interest. Our discovery studies have shown this for all the topics examined, even though we have uncovered much discovery in literatures related directly to the problem literature of interest. Discovery from directly related literatures tends to be from substances or topics in lower frequency published areas.

We also find that much more potential discovery is possible from literatures related indirectly to the problem or topic of interest. In this case, because of the additional linkages between the concept being researched and the problem of interest, the connections may be more difficult to identify, and the concept researchers may be less aware of the linkages. We believe the focus of much of the ODS LRD community on directly related literatures has reduced the possibility of finding much potential discovery.

The second fundamental assumption has some overlaps with the first. It is used by some ODS LRD researchers in ranking potential discoveries. It is based on the occurrence frequency of a potential discovery concept in literatures related to the problem literature compared to the concept's relative occurrence frequency in all of Medline. It can be interpreted as more research in a related area provides greater confidence that the potential discovery concept's impact will be real and not spurious. While this idea certainly has merit, it runs counter to our argument on the foundational assumption above. The larger the number of researchers in a related area,

the greater will be the chance that at least one researcher will be familiar with the target problem of interest. We believe the emphasis on high frequency phenomena in the priority ranking schemes has reduced the possibility of finding much potential discovery.

The third fundamental assumption is also frequency related. It is founded on the idea that the more pathways by which a potential discovery can impact the problem of interest, the higher the chances that at least some of these pathways will be valid, and the higher should be the priority or ranking of the proposed discovery. We have argued in Chapter 1 (also see [6]) that unless the final treatment for a given disease is known a priori, or at least the characteristics of the final treatment are known (e.g., one substance, multiple substances), invoking this quantitative pathway metric could be very misleading and could effectively eliminate potential discovery.

However, we should not underestimate the importance of substances that impact a number of problem characteristics. For example, dehydration (water deficiency) will result in a number of symptoms, and correction of this deficiency will eliminate the multiple symptoms. For this type of causal situation, substances that impact multiple symptoms should certainly receive high consideration. This is a different statement from requiring that number of problem characteristics impacted be imposed as a generic filtering condition. We believe that use of this quantitative pathway assumption has reduced potential discovery, although probably not to the same extent as the first two fundamental assumptions.

## 2c. Commonality of Potential Discovery for Medical Treatments

The three most recent medical studies (Cataracts, PD, MS) were conducted using a streamlined approach, based on extensive use of MeSH terms and semantic categories. In evaluating the potential discoveries generated for these medical problems, it appeared that the discoveries could be classified into two categories: those unique to the particular disease and those in common with the different diseases. The uniqueness or commonality was a strong function of the query employed.

In deriving the directly related literature queries for each of the three medical problems, we analyzed the clusters of the core literature, and focused on the main medical phenomena typically associated with the specific medical problem. Thus, for the cataracts query, the focus was on

protein degradation in the lens, and the query terms reflected this emphasis (e.g., protein degradation, protein glycation, protein aggregation). For the PD query, the focus was on the early death of dopaminergic neurons and the formation of Lewy bodies; for the MS query, the focus was on myelin sheath destruction/axonal loss and blood-brain-barrier disruption. These direct query terms focused on some type of degradation associated with the disease, and could be interpreted as symptoms/characteristics of the disease. The direct query terms tended to be disease unique, although there was some overlap between two diseases in a few terms (e.g., Cataracts and PD: protein degradation, protein aggregation, protein oxidation).

In deriving the indirectly related literature queries for each of the three medical problems, we analyzed the clusters of the directly related literature, and focused on the main medical phenomena that resulted. While many cluster themes and associated key phrases were again medical problem unique, there were some cluster themes and associated key phrases common to all three medical problems. These themes were focused on ‘oxidation’, and were associated with MeSH/text phrases such as Oxidative Stress, Oxidative Damage, Reactive Oxygen Species, Free Radical Scavengers, Oxidation-Reduction, Antioxidants, and Free Radicals. These common themes/terms could be interpreted as one step closer to causes of the disease. Because of query length considerations, not all these common terms were added to all the indirect queries, but had these limitations not existed, all the common oxidation-related terms above would have been present in all the indirect queries.

Because of the specificity of the direct query terms and the generality of the indirect query terms, the indirect retrievals tended to be much larger than the direct retrievals. In addition, because of their generality, the oxidation-related terms tended to be a significant portion of the indirect retrieval. To reduce the volume of the indirect retrievals, we used combinations of query terms as a semantic filter.

The practical consequences of all the indirect retrievals for the three medical problems having significant contributions from the oxidation-related query terms/records are that a reasonable fraction of potential discoveries will be in common for the three medical problems. Thus, if substance X is shown to reduce oxidative stress, it could be applicable to any of the three diseases above, although its weighted impact might be quite different for each

disease. Or, if substance Y is shown to increase oxidative stress, it could also be applicable to any of the three diseases.

## 2d. Effects of Synergistic Discoveries/Treatments

Most of these potential discoveries we have identified, or have been claimed by other ODS LRD researchers in the open literature, are based on effects from single concepts, substances, or lifestyle changes. They could be termed ‘potential individual discoveries’. Any synergistic effects resulting from combining these concepts, substances, or lifestyle changes have not been researched. **There is no reason to exclude combinations of individual potential discoveries as potential discoveries in their own right.** They could be termed ‘potential synergistic discoveries’.

In fact, we believe synergistic effects may be of extreme importance in realizing the value of the individual discoveries identified in this monograph. What leads us to this belief? Appendix 4 of this monograph contains some articles uncovered in the present medical studies displaying evidence of dramatic effects resulting from synergies that would not result from individual substances taken in isolation. **We believe these findings are endemic to the total medical literature.** Appendix 5 of this monograph contains a few examples of powerful synergies extracted from other segments of the medical literature. Thus, for the medical applications, synergistic effects of individual discoveries could be very important in determining optimal treatments.

There is also benefit (for the medical applications) in identifying synergistic effects of individually harmful substances or lifestyles. For example, as shown in the last section, suppose substance X results in increased oxidative stress, and increased oxidative stress is a factor in any of the three diseases. Then, a recommendation to avoid substance X could have multiple impacts. Suppose substances X, Y, and Z were shown to have synergistically harmful effects on oxidative stress. Even more powerful recommendations could be made if these synergies could be identified. Of course, the magnitude of the adverse synergistic effects could vary across diseases, and across individuals with these diseases (depending on their genetic makeup). Understanding these effects takes us one step closer to making perhaps universal recommendations.

Unfortunately, synergies are very difficult to analyze, but that is no reason for their neglect. Kostoff and Delafuente [7] show that, for the case of drug combinations, the number of potential combinations of individual drugs is enormous for more than a few drugs. The same computations can be used to show that the number of combinations of individual potential discoveries is enormous for more than a few individual potential discoveries. The studies described in this monograph (and in the published ODS LRD literature as well) address the effects of individual concepts, substances, or lifestyle changes only. These studies do not address the potential effects of combinations, or the large number of laboratory studies and clinical trials that would be involved in uncovering the efficacy and safety considerations of these combinations.

## 2e. Exploitation of LRD

To determine how effectively the potential of ODS LRD was being exploited, we conducted a detailed survey of the total ODS LRD literature [8]. Based on our discovery definition, we saw very few, if any, results from ODS LRD that we would classify as potential discovery. This was due to two reasons. First, the methodological concepts used to identify discovery were mainly quantity-based information science approaches, whereas the main component of discovery is quality-based. In other words, the techniques were not focused on targeting the characteristics of discovery, but on applying information science approaches. Second, the potential discoveries claimed were shown, upon proper vetting, not to be discoveries by our definition. Either prior art existed in the mainstream medical literature (all prior ODS LRD studies were medical), or in the cases where prior art did not appear to exist, the linkages identified were judged to add minimal value.

In our background reviews for the specific medical studies we performed, we accessed 1) the premier medical Web sites and 2) prestigious academic and clinical reviews in the peer-reviewed literature. We found this mainstream medical literature focused almost exclusively on treating symptoms, not addressing causes. The focus was on employment of drugs and/or surgery for most of the medical problems we examined.

We searched Medline and the SCI to identify a core literature for each disease studied (where the potential treatments (non-drug) were mentioned in the same article as the disease) and potential discoveries (where the



potential treatments were not mentioned in the same article as the disease). We found there was almost a complete disconnect between the contents of the core medical literature we uncovered and the mainstream medical literature. For the most part, in the mainstream medical documents we examined, the core literature potential treatments were not even mentioned as supplements to the standard medical treatments, much less as potential replacements for the standard medical treatments.

We also found the core literature was somewhat fragmented. There were no comprehensive articles that systematically identified the core non-drug literatures for each disease, identified patterns in these literatures, and provided a comprehensive picture of what is available in the core. Even though providing a comprehensive picture of the core literature is not ODS LRD, we believe it has substantial value, and we may pursue this comprehensive core assessment as a spin-off of our research.

Finally, there is the question of potential discovery implementation. While this issue may appear superficially to be beyond the proof-of-principle demonstration scope of this monograph, we believe it may be endemic to any type of ODS LRD conducted properly. Voluminous discovery may be the norm resulting from a number of ODS LRD studies, and the present analysis would be somewhat deficient without addressing the implementation issue implications to some degree.

We generated a large amount of potential discovery, and believe we only saw the tip of the iceberg of what is available. How does one handle these large amounts of potential discovery? We did not see this issue addressed in any of the ODS LRD papers we examined, since most of the ODS LRD researchers were at the other end of the discovery spectrum: struggling to find even a few potential discoveries. The following section summarizes briefly the implementation issue.

### **3. DISCOVERY CAPITALIZATION STRATEGY**

Most of the potential medical discoveries we identified were individual (typically substances), although there were some synergistic combinations shown. For the full scope of our findings to be considered for implementation, not only would individual substances need to be tested, but combinations as well to check for potential synergies or antagonist effects.

What would this mean in practice? Assume an adequately resourced medical study identified 300 potential discoveries. Assume further that a workshop of experts was convened, and the participants concluded that 50 of these potential discoveries were high priority, and all needed further testing before they could be recommended for therapeutic purposes. To test the potential discoveries individually, probably a couple hundred field trials would be required. This is not a small or inexpensive undertaking, but it is theoretically doable.

To test the potential discoveries in combination, much more effort is required. Assume, for example, that combinations of potential discoveries up to ten were of therapeutic interest. Then, according to [Kostoff and Delafuente, 2006], the number of combinations is the binomial coefficient  $(n!/((n-r)!*r!))$ , where  $n$  is the total number of potential discoveries, and  $r$  is the maximum number in each combination. For the case at hand ( $n=50$ ;  $r=10$ ), the number of combinations is  $(50!/(40!*10!))$ , or 10,272,278,170 (approximately ten billion), and the number of field trials required is probably four times that amount. Obviously, this is completely unrealistic. But even for all combinations of two ( $\sim 1250$ ), approximately 5000 field trials would have to be run. Even in a case of much smaller numbers of potential discoveries and combinations (e.g.,  $n=25$ ;  $r=5$ ), the number of combinatorials is still prohibitive (53130).

Our findings here parallel the findings in Kostoff and Delafuente [7] for the case of drug combinations. The numbers of field trials required to check for positive or negative synergistic effects are unrealistic. In the case of drugs, combinations are prescribed based on safety and efficacy of individually tested drugs. Perhaps the same philosophy will have to be adopted for implementing potential discoveries for treating RP or any of the other diseases studied with ODS LBD.

## 4. LESSONS LEARNED: DISCOVERY PROCESS STEPS

### 4.1 Background

The flow chart (Figure 1) displays the portion of the discovery process that starts with the development of the core literature query and ends with analysis of the potential discovery from the indirectly related literature. It was developed iteratively, and refined as a result of each study conducted.

However, before the development of the core query is initiated for any study, there is substantial background effort required. This background work provides context for conduct of the study, especially for developing a strategy of how to proceed with the discovery results. In all five topical studies, there were two major background efforts performed: a) identifying the mainstream topical literature and reading it to understand the topical issues; b) conducting an invited review of the ODS LRD literature [8].

There were two main sources for identifying the mainstream topical literature. One source was the major medical and/or technical Web sites. We examined on the order of ten premier Web sites for each study. The other source was review papers (typically, but not always, academic) of the topic, published mainly in the peer reviewed literature, but sometimes in book chapters. We summarized the mainstream literature for each topic, and placed it at the front of each study write-up.

In conducting the review of the ODS LRD literature, we examined the major ODS LRD publications over the past two decades, and identified strong and weak points. The aim was to use the strong points for enhancing our process. Our interpretation of the literature was that **none** of the ODS LRD concepts were intrinsically geared toward identifying discovery, and none of the discoveries claimed were potential discoveries. We took these findings into account in designing our process diagram, in hopes of eliminating the problems we believed were inherent in the other ODS LRD approaches.

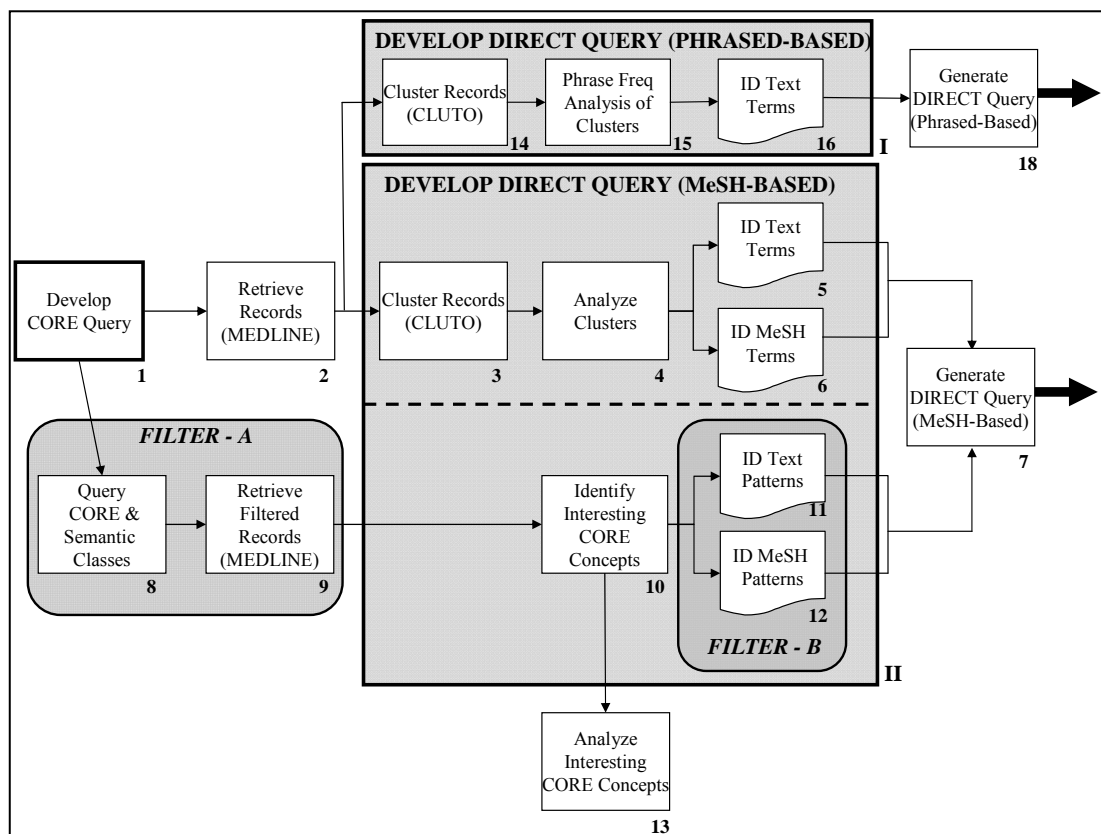
### 4.2 Discussion of the discovery process

The process flow chart shown in Chapter 2 (also see [9]) will be used to focus the presentation of the main discovery process steps presented here. The alphanumeric strings used in this section identify the location on the flow chart being discussed. In the discussion, the number format will be of

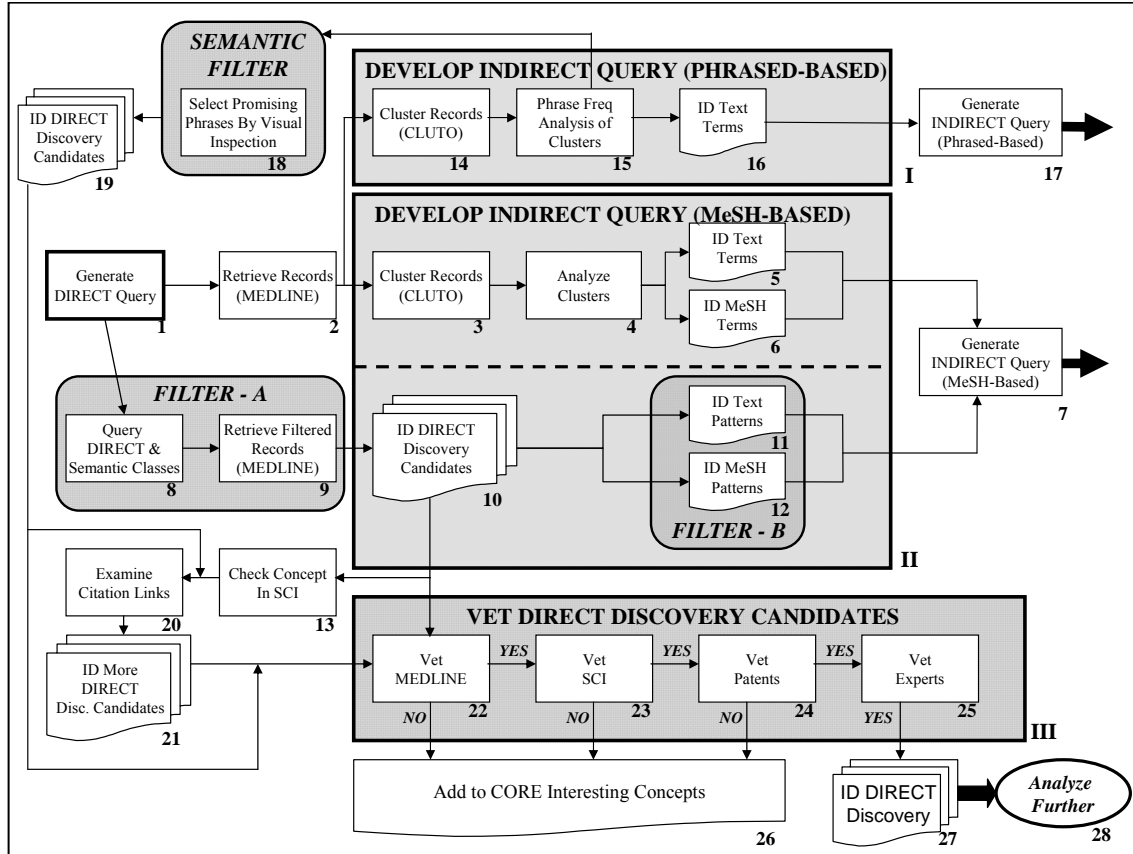
the form X-ij. There are three frames that comprise the flow chart, and they are labeled frame A, B, and C. Therefore, the first character in the string (X) will be either A, B, or C, and will refer to the specific flow chart frames being discussed. The remaining numbers in the string (ij) will refer to a specific block on the frame selected.

FIGURE 2 FROM [9]  
(MEDICAL DISCOVERY PROCESS FLOW CHART)

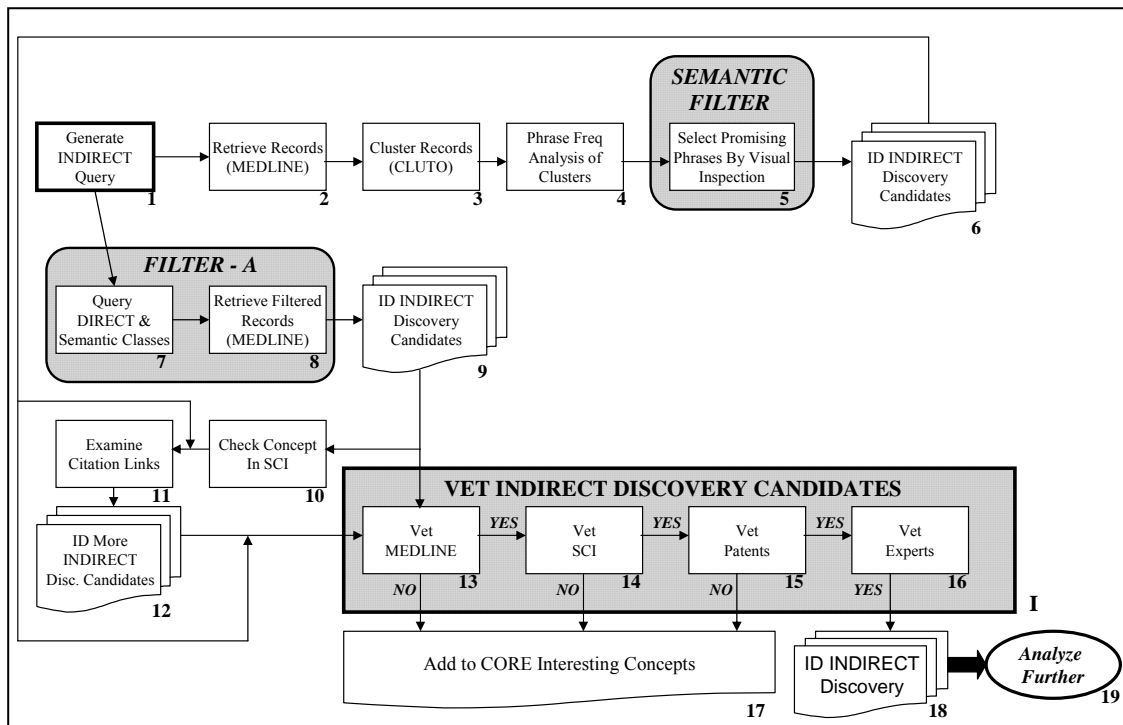
### FRAME A



## FRAME B



## FRAME C



### 4.2.1 Core Literature Generation

#### A-1---A-2 Core Query Development/ Core Literature Retrieval

Use of text terms that were also MeSH taxonomy terms (e.g., Raynaud Disease, cataract\*, Parkinson's Disease, Multiple Sclerosis) allowed the medical core queries to be very short. The non-medical (WP) core query was very long and required months to develop. Our Simulated Nucleation technique [10] allows core queries consisting of hundreds of terms to be generated straight-forwardly. Additionally, multiple relevant databases consistent with available resources are desirable, as well as the largest time frame for data availability. Record retrieval was straight-forward in all cases.

### 4.2.2 Generate Directly and Indirectly Related Literatures

#### 4.2.2.1 Streamlined Approaches (Cataracts, PD, MS)

### A-3---A-6/ B-3—B-6 Record Clustering and Analysis

To maximize chances for finding potential discovery in the expanded literatures (directly related when starting from the core literature; indirectly related when starting from the directly related literature), all the diverse major topical themes of the starting literature should be represented in the expanded literature. To insure this occurs, a grouping of records or phrases in the starting literature is required, and expansion can then be performed about every major theme.

We tried different grouping/clustering techniques including phrase clustering (for the early phase of the RP study), document clustering (all studies), phrase auto-correlation maps (MS study), and phrase factor matrices (MS study). We recommend that multiple grouping/clustering approaches be used in future studies. Each grouping method contains its own unique groupings, which can serve as a rich source of query phrases/phrase combinations.

In particular, for the final medical study (MS), we used document clustering, phrase auto-correlation mapping, and phrase factor matrix analysis. While there was much commonality in results among the methods, there were sufficient differences to generate value added for each approach. We recommend at least these three clustering approaches for future discovery studies.

Because we were time and other resource limited in the medical studies, we used relatively small numbers of clusters for analysis, which meant relatively large cluster sizes. This limited the types of phrases for analytical purposes to somewhat general descriptors. In more comprehensive studies, many more clusters could be used (as was done in the WP study). Each cluster would be more focused. This would allow access to lower frequency, longer, and more detailed mechanism-focused phrases. If a hierarchical taxonomy document clustering algorithm is used, the more generic phrases can be obtained from the higher level (aggregated) clusters and the more detailed phrases can be obtained from the lower level clusters.

During the MS study [4], we ran some brief experiments with the Arrowsmith software [11]. Arrowsmith typically operates in a closed system discovery mode, but we ran it in a quasi-open system mode. Arrowsmith requires two input literatures: in a quasi-open system mode, one

literature is the ‘problem’ literature’ (MS in the present case) and the other literature is the ‘solution’ literature (the non-drug semantic classes in the present case). Arrowsmith generates the intermediate literature, which is basically a phrase list common to titles in each literature. The operational challenge is that, depending on the sizes of the two literatures, thousands or tens of thousands of intermediate literature phrases could result. These numbers apply to titles; if Abstracts were used, the number of intermediate literature phrases would increase substantially. Some method of downselection of intermediate phrases is required.

The method we used for downselection was based on clustering. We had clustered the core and directly related literatures before using Arrowsmith, and we had some understanding of which thematic intermediate literatures should be searched. We identified the theme of each cluster, and the key phrases within each theme. We searched for those phrases, or very similar phrases, in the list of intermediate literature phrases in Arrowsmith, and were able to generate potential discovery immediately.

In summary, no matter which discovery identification method we selected, the use of clustering and subsequent analyses added rigor to accelerating the discovery process.

For the medical studies specifically, the document clustering algorithm yielded both text and MeSH terms in each cluster. The text analysis software [12] used in the MS study showed text and MeSH patterns in records through phrase auto-correlation mapping and phrase factor matrix analysis. These patterns provided a foundational basis for future combining of text and MeSH phrases in the query.

#### A-8---A-12; B-8---B-12 Semantic Filtering; Streamlined Approach

In parallel with steps A-3---A-6 and B-3---B-6, which identify phrases and their patterns based on grouping in the *unfiltered* core retrieval, steps A-8---A-12 and B-8---B-12 identify phrases and their patterns based on *semantic filtering* and manual selection in the core and directly related literature retrievals. For all the medical studies using the streamlined approach, we intersected the core query (Frame A) and directly related literature query (Frame B) with non-drug MeSH classes to generate records in which non-drug substances were typically researched as potential treatments. We examined the potential discovery candidates in the retrieved literatures for



text and MeSH term patterns, typically groups of terms that co-occurred. We found that there were distinct patterns in the potential discovery candidates that did not exist in the remainder of the records. In the potential discovery candidate records, there tended to be multiple MeSH terms in the thematic groups defined by the clustering algorithm, whereas in the other records there may have been one or no MeSH terms in these thematic groupings. Moreover, in the potential discovery candidate records, these multiple MeSH terms tended to group intra-theme, although there were exceptions where inter-theme MeSH terms were observed. We noticed the intra-theme grouping in the final MS medical study [4], then subsequently verified that it also occurred in the previous cataracts and PD medical studies. The text and MeSH patterns we identified complemented the patterns found in the clustering pathway, and served as the basis of a semantic filter based on characteristics of prior discovery.

Because recent articles in MEDLINE were not indexed with MeSH, and not all appropriate MeSH terms were assigned to each remaining article, some concepts that were potential discovery probably did not appear, and some concepts were retrieved that already existed in the core literature.

#### A-7, B-7 Generate Direct and Indirect Queries

These steps were two of the more challenging steps of the entire process. They were also two of the most important steps, since the comprehensiveness and precision of the retrieved data were directly dependent on the quality of these queries. No level of sophisticated data analysis could compensate for data deficiencies.

There were two separate pathways leading to these steps (as described above), resulting in four sets of phrases and patterns, as well as one group of clusters from the document clustering, another group of factors from the factor matrix, and a final group of thrusts from the phrase auto-correlation maps. The phrases ranged in size and scope from (typically) short and very general high frequency to (typically) long and very specific low frequency.

The first decision point on query definition was which medical/technical themes to retain for the literature expansion (core → direct expansion, or direct → indirect expansion). For the query expansion from the core literature to the directly related literature, we tended to retain themes characteristic of the central problem (e.g., protein aggregation for the

cataracts problem; dopaminergic neuron apoptosis and Lewy bodies for the PD problem; demyelination for the MS problem) rather than the more generic characteristics. These phrases could be viewed as ‘symptoms’, as observables in the sense of macro-level biomarkers. For these diseases, one ‘sees’ opacification of the lens, dead dopaminergic neurons and Lewy bodies, myelin sheath degradation. For the query expansion from the directly related literature to the indirectly related literature, we tended to select the new terms that appeared from the groupings (e.g., oxidative stress, lipid peroxidation, enzyme activation), which were the next step removed from the central problem. These more generic phrases could be viewed as ‘causes’, or at least as one step closer to causes. While substances like smoking or dairy could be viewed as actual causes in some of the diseases, their fundamental impact could be translated into terminology such as ‘oxidative stress’.

The second decision point was which type of phrase to retain for the query. Very generic phrases would retrieve too many records, and very specific phrases would retrieve too few. The specificity of the records retrieved at these extremes would, on average, be different as well.

One school of thought opted for using specific phrases, and more of them. These types of phrases would retrieve records where more specific mechanisms were identified, and the resultant potential discovery would have increased credibility because of its links to a specific mechanism rather than to a generic mechanism. While there is merit in this perspective, potential problems exist. There is little consensus on the proper use of terminology in the scientific literature. In emerging scientific fields especially, there is relatively little consensus on the use of terminology compared to that in mature fields. Therefore, use of very specific terminology in searching emerging scientific fields will probably result in severe under-retrieval because of the diverse use of terminology to represent the same concept. Only in mature fields will there be more common use of specific terminology to represent the same concept; these mature fields may not be the best choice when looking for radical discovery. To cover these emerging fields, more general MeSH terms would insure that new concepts would have a better chance of being accessed by the query.

As the medical studies progressed, we tended to select larger numbers of phrases, with the bulk being moderately specific and some being more generic. In a sense, we hedged our bets, to insure that we accessed concepts

from new fields as well as more specific mechanisms that would be impacted. Based on the pattern analysis of the Abstract text and MeSH phrases, we tended to use combinations of terms for the queries. For the most specific phrases, we used the phrases by themselves (combinations of one). For moderately specific phrases, we used all combinations of two combinatorially. For the more generic phrases, we used all combinations of three combinatorially. If we had to mix specific and generic phrases, we iterated the number combined by examining different retrievals. As a rule of thumb, the more generic phrases tended to be selected from the MeSH term patterns. This is not surprising, since there are relatively few MeSH terms (~22500), and as a consequence they tend to be much more generic than Abstract text phrases.

One note of caution. When combinations of terms are used in a query, they serve as filters. There is always the danger that potential discovery candidate records could be removed. Intra-theme combinations probably serve as weak filters (if at all), but inter-theme combinations begin to approach Swanson's multiple pathways priority ranking assumption discussed earlier, and could serve as strong filters.

Especially for combinations of three or more, these tend to be somewhat restrictive. We did not have a problem with combinations of three: the studies reported here were demonstration studies, not production studies, and we generated far more potential discovery than we could handle. However, if we were doing adequately resourced quasi-production studies, we would probably make the tradeoff in favor of recall rather than precision. Given the importance of these medical problems being addressed, where billions of dollars have been spent in trying to identify treatments or 'cures', any potential treatments should be identified, even if additional time is spent sifting through large numbers of records generated by more expansive queries. We would probably have selected combinations of two in those cases where we had combinations of three, if nothing more than to insure that no promising potential treatments were overlooked.

Initially, we allowed phrases from different medical themes to be combined for the combinatorial groupings. This tended to retrieve some records that covered multiple disciplines. Closer examination of the text and MeSH patterns in the interesting core documents showed that the bulk of these records tended to have intra-discipline combinations, reflecting mainly a single discipline focus.

For the MS study, we used the different approaches to identify how the text phrases and MeSH phrases tended to group (clustering, autocorrelation maps, factor matrix). Most groups were intra-discipline, but not all. We reflected this reality by restricting the combinatorial combinations to intra-theme mainly, but not completely. Any intra-theme combinations were based on relationships identified in the grouping analyses. Especially for phrases of moderate specificity, these allowed reasonable retrievals to be obtained. Had we used inter-theme combinations for phrases of this level of specificity, relatively few records would have been retrieved.

Obviously, the whole process of term selection and combination needs more theoretical work in parallel with parametric studies, to develop a more systematic approach to the query development process.

#### 4.2.2.2 RP Approach

##### A-1---A-2 – Core Literature Retrieval

The RP core literature was developed and retrieved the same as described above for the streamlined approaches.

##### A-14---A-18; B-14---B-17 – Generate Direct and Indirect Queries

The RP study was performed with minimal assumptions and shortcuts. In particular, it did not contain the two semantic filters A and B shown on Frames 1 and 2. To generate the direct and indirect queries from their respective starting queries and literatures (core query and literature in the direct case; direct query and literature in the indirect case), a clustering of the starting literature was performed. Then, once the main themes had been identified (blood viscosity, platelet aggregation, vasoconstriction), the queries for each theme were developed from the cluster theme phrases and from an iterative relevance feedback approach [10]. While selected phrase combinations were identified for each query, a combinatorial approach selecting all combinations (as in the streamlined approach) was not used.

The expanded literature generated was adequate for the study. Newer and more detailed approaches to literature expansion (beyond the clustering mentioned above) have been developed since the RP study was performed

and completed. We believe that a much larger expanded literature is possible with these new expansion approaches.

Additionally, these new expansion approaches involve going beyond the literatures related directly to the core (such as the blood viscosity literature) to the literatures related indirectly to the core (such as non-blood viscosity literature). For the RP problem, this additional expansion was done for only one of the three directly related literatures (blood viscosity). The blood viscosity literature was the smallest of the directly related literatures, and yielded a modest indirectly related literature. Expansion of the platelet aggregation literature and vasoconstriction literature to indirectly related literatures would have yielded a massive increase in the expanded literature. Our experience with the other expanded literatures showed that every time a new expanded literature was analyzed, substantial additional potential discovery was generated. We believe this additional discovery would have continued had the additional expansions been performed, and would have been substantial because of the potential magnitudes of the additional expanded literatures. This additional expansion was not done because of the resource limitations of the study.

We believe that the expansion to indirectly related literatures contributes to potential discovery both quantitatively and qualitatively. The quantitative contribution to discovery results from the sheer volume of additional candidates in the indirectly related literatures. The qualitative contribution, which may be the most important in the long run, is based on the following argument.

We believe that the more directly related the expanded literature is to the core literature, the easier it is to identify potential discovery. On average, we believe the discovery so identified will be incremental, not truly radical. This conclusion is truer as the frequency of potential discovery phrases in the directly related literature increases. Intuitively, the more people working on a potential discovery topic in a directly related literature, the greater the chances they will be aware of the linkage to the core literature, and the less the chances for radical discovery.

As the expanded literature becomes more remote from the core literature, then the chances that researchers in the expanded literature are familiar with core literature problems decrease, and more radical discovery is possible. At the same time, identification of the linkages between the potential discovery

and the core literature becomes more difficult. Thus, we have the paradox that truly radical discovery becomes more possible as the core and expanded literatures become more disparate, but the identification of that potential radical discovery becomes more difficult as these literatures separate.

#### 4.2.3 Generate and Validate Potential Discovery

##### 4.2.3.1 Streamlined Approach

###### B-10; C-9 Identify Potential Discovery Candidates

This step was relatively straight-forward. It involved reading all the semantically filtered records, and, for each record, making the judgment whether it appeared to be a potential discovery candidate. For the filtered records from the directly related literature, this did not present much of a problem. With the queries restricted to focusing on the quasi-‘symptoms’ characteristic of the main thrust, and the records restricted to non-drug classes, the number of records retrieved was in the low to mid-hundreds in all cases. In a more comprehensive study, where more medical thrusts and terms might be used in the query, and where the number of semantic classes would be expanded, the number of directly related records would increase. However, in adequately resourced studies, reading these records would not be problematical.

For the filtered records from the indirectly related literature, the number of records proved to be problematical. There typically was at least an order of magnitude more records in the indirectly related literature compared to the directly related literature. Time became a major evaluation factor.

For an adequately resourced study, where many more records would be available for potential discovery, the discovery identification processes developed for the Water Purification study [5] could be used as a time-saving alternative to reading all the records retrieved. The Cluster Semantic Filtering approach would, for example, cluster the thousands of indirectly related records. Visual inspection of the cluster themes would identify those that appeared most promising, as was the case in the Water Purification study. Then, each record in the promising clusters would be examined for discovery potential. The Latent Semantic Indexing (LSI) approach [5] would start with interesting core records and identify records in the related literatures similar conceptually but with different terminology.

One alternative we investigated was using very detailed terms in the indirect query to replace the more generic terms, albeit more of these detailed terms. While the number of records retrieved decreased sharply, we were concerned that potential discovery from emerging fields could have been lost due to the emerging field/mature field terminology issue discussed previously. Our present perspective is to add some specific terms to the indirect query, but not to the full exclusion of some of the more generic terms. We are willing to sacrifice precision for recall, in problems as serious as the ones we are studying.

#### 4.2.3.2 RP Approach

##### B-18---B-19; C-5---C-6 Identify Potential Discovery Candidates

After retrieving the directly and indirectly related literatures, we performed a phrase frequency analysis on the total RP retrieval. There were about 271000 phrases (single, double, and triple adjacent word phrases) with a frequency of two or greater, and almost 900000 phrases with a frequency of unity. We inspected visually about 271000 phrases (with a threshold frequency of two) from the expanded literature, and selected about 1000 phrase-literature combinations for further inspection. In a major break with other ODS LRD approaches, we used no numerical filters to eliminate any phrases. The only restriction imposed was that promising discovery phrases would come from non-drug categories, a restriction similar to that imposed by Swanson in his initial RP paper. This restriction could be viewed as the analog of the semantic filters described previously, performed manually rather than through MeSH. We believe it was the removal of the numerical filters and the examination of all the phrases in the expanded literature that resulted in the massive increase in potential discovery of our approach relative to all previous ODS LRD approaches on the RP problem. All the previous numerical filters, for which there were no theoretical bases, probably eliminated much of the discovery in the process of winnowing down the numbers of phrases to be evaluated in detail.

Despite the additional discovery generated by our approach relative to previous approaches, there were two major limitations on our approach. First, we did not examine the 900000 phrases with a frequency of unity because of time and resource limitations. It is our belief that potential discovery will derive from low frequency events (as stated previously).

Therefore, if there are many people working on a potential discovery topic, the chances decrease that none of the researchers will remain unaware of the link to the core problem area. We believe that a large source of potential discovery was excluded by not examining the unity frequency phrases.

Second, the selection of candidate discovery phrases for further examination was conducted by non-medical personnel, due to resource limitations and allocation of responsibilities. More generally, use of non-experts in text mining discovery is almost unavoidable, since the foundations of the approach are based on examining a broad range of literatures very disparate from the core problem literature. Unless resources are available to employ experts from all the disparate discipline literatures accessed, non-experts will be used by default. Presently, we have no estimate of the seriousness of using non-experts as part of the text mining discovery process?

In the case at hand, use of non-medical personnel to conduct text mining discovery for medical problems can be viewed from multiple perspectives. Swanson addressed this issue in a study on linkages between Magnesium and Migraine [13], as follows. “Expertise in all specialties is not a prerequisite for seeing new connections. My own ignorance underscores this point, for better or worse. Being neither physician nor physiologist, I do not bring to this review any medical knowledge that goes beyond what is obvious in the literature I cite; my purpose has been to assemble the ideas of others , like putting together a puzzle – albeit a puzzle with some unknown number of missing pieces.”

Our experience offers a different perspective. We will combine our experiences in identifying candidate discovery phrases and evaluating articles containing those phrases for potential discovery in the present discussion. For phrase selection, the more obvious phrases that fall within the desired categories (food, food derivatives, lifestyle factors) for the RP problem can be identified by experts and non-experts alike. For identifying articles that contain potential discovery, the potential discovery articles that are related most directly to the core literature can be identified by experts and non-experts. For example, an article that describes experiments where EPA-rich diets were fed to humans and resulted in decreased platelet aggregability would be obvious as a ‘discovery’ to readers with different levels of medical expertise.



The problem arises when phrases and concepts that are related to the core literature more remotely are present. In these cases, the non-direct connections from these remote literature phrases are more subtle. They tend to involve more mechanism-mechanism connections, and in many cases would require an understanding of biomedical mechanisms in order to establish the connections. As we have stated previously, we believe these remote linkages would have the highest probability as sources of radical discovery. In Swanson's approach, mainly directly related expanded literatures were examined. The linkages could be identified by non-experts, although Swanson severely understates his capabilities when he refers to himself as a non-expert (non-credentialed does not equate to non-expert).

Therefore, we believe that to generate the most radical discovery, medical experts are required to participate in both the phrase selection step and the linking of the candidate articles to the core literature step. Medical expertise was used to validate the latter linkages in our study, as well as in all steps leading to the expanded literature. More discovery (perhaps much more), and more radical discovery would be possible if medical expertise were used in all the steps of the process.

### 4.3 Citation Linking

#### B-13, B-20---B-21; C-10---C-12 – Citation Linking for Additional Discovery

In the relatively few cases where citation linking was used for discovery, it appeared very promising. However, there are many types of citation links that can be examined. Some may involve examination of hundreds or thousands of records. The main issue is which type(s) of citation linking to use to search for potential discovery, and what is the cost-benefit of each approach..

In those cases where we started from a potential discovery candidate, then used the Related Records feature of the SCI (identify records that share common references with the starting record), there were many cases where thousands of related records were identified. We selected only those that had the most shared references. This will offer some assurance that the related records obtained are similar to the potential discovery candidate, and therefore have a higher chance of being potential discoveries themselves. Other types of links need to be evaluated individually for efficient selection

approaches. We did not examine these other linking approaches sufficiently to draw conclusions about optimal discovery search strategies.

#### 4.4 Vetting

##### B-22---B-25; C-13---C-16 – Vetting of Potential Discovery Candidates

Vetting of potential discovery candidates is critical for establishing credibility of results. Many of the ODS LRD studies we examined for the background review had insufficient vetting criteria, in our estimation. The four-step vetting process we established should be viewed as a threshold. For ODS LRD studies in which discovery patents are desired, far more vetting would be required. Many more literatures would have to be examined than the few utilized here. For every ODS LRD paper published, the vetting process and databases used should be an integral part of the reporting.

The main issues in vetting are which literatures/databases to vet, the breadth of the synonyms that can be vetted, and for MeSH terms, what is the depth of proxy terms that can be used and are within the purview of the MeSH terms employed. For the patent database, the problem is compounded by the (typically) broad scope of the claims. Claims that appear to impinge on potential discovery candidates need to be examined for validity, to ascertain whether a basis for the claim has been established.

#### 4.5 Literature-Assisted Discovery (LAD)

In the ODS LAD experiment, we identified experts from the related literatures, and sent them notification of a Broad Agency Announcement (BAA) posting on WP. We hoped this would stimulate submission of proposals from technical disciplines not normally associated with WP. Approximately 2/3 of the ~300 pre-proposals received were of this nature.

We view these results as the tip of the iceberg. As far as we know, this was the first of its kind experiment. It was not a planned experiment/study, but rather resulted from a target of opportunity.

The core and expanded queries were being developed for another study. An iterative process was being used for query development. The idea for the experiment arose relatively close to the deadline for BAA posting. In order

to meet the deadline, the final query iteration was not performed. As a result, the query contained more ‘noise’ than the final query that eventually resulted for use in the other study.

This imperfect query had two consequences. First, some of the experts in disparate disciplines who should have been reached were not reached, and some experts in disparate disciplines whose areas of expertise had no relation to the topical matter, even indirectly, were reached. Second, there was an insufficient period for the recipients from disparate disciplines to formulate proposals that reached across disciplines. Normally, when experts in the topical field of a BAA receive notice of a BAA, they can respond rather quickly, because they are intimately familiar with the topical matter and potential solutions. However, for experts not in the topical area of the BAA (WP, in our case), a ‘gestation’ period is required in order for them to be able to translate their non-WP concepts into ideas applicable to WP. We believe an insufficient gestation period for these disparate discipline experts existed, with the consequence that not as many proposals were generated as could have been with a longer gestation period.

We believe that an order of magnitude more proposals could have been generated (compared to the previous year’s BAA when only the discipline experts were notified of the announcement) had a finalized query been generated, had a longer gestation period been allowed, and had the rationale for the incorporation of the disparate discipline experts on the distribution list for the announcement been clearer. An upcoming similar experiment will integrate these lessons and hopefully avoid the inefficiencies that resulted from the initial experiment. Nevertheless, we want to emphasize that the initial experiment:

- was successful,
- accessed ideas from very disparate literatures,
- provided a powerful option for Federal agencies to obtain proposals that could lead to radical discovery.

## **4.6 SUMMARY**

In summary, we have generated substantially more potential discovery than all the other reported studies on the RP problem combined. We believe we are also the first group to have generated true potential discovery, and large

amounts of this potential discovery, for treating PD, MS, cataracts, and for improving WP as well.

This large discovery is due mainly to our removal of the numerical filters used to reduce the number of potential discovery candidates required to examine. The cost of this added discovery was visual examination of a large number of phrases for candidate discovery phrases in the RP study (visual semantic filtering), and the subsequent requirement to examine the many articles retrieved that contain these phrases. For the other medical studies, the cost was visual examination of substantial numbers of records for candidate discovery. Further, we have uncovered only the tip of the discovery iceberg in all the studies performed. Much more discovery on the RP problem is possible by

- More comprehensive expansion of the core literature by using larger queries
- Involving more biomedical personnel in the discovery identification process who are equipped to identify the more subtle relationships
- Examining the ~900000 phrases with a frequency of unity for potential discovery. From the rare event perspective discussed previously, these rare phrases may have the most potential for *real* discovery! Coupled with a more complete expanded literature, the unity frequency phrases could total well over a million, and serve as a veritable ‘gold mine’ for real discovery
- Using the citation-based discovery pathways more extensively, since these pathways offer enormous potential for discovery
- Improving the information content of records (not under our control). Many records contained insufficient information to make a determination of discovery. Almost all records prior to 1975 did not contain Abstracts, and a significant number of records in the decade after 1975 also did not contain Abstracts. Because of the large volumes of papers without Abstracts, it was not feasible to track down the full texts of these papers. Unless a positive determination of potential discovery could be made, an item was not included in the discovery list

The above bullets hold true for the other medical studies as well, with the exception that the bullet about phrases would be replaced with a bullet about expanding the semantic classes examined. To capture the benefits of the text

based approach used for the RP study and the MeSH based approach used for the other medical studies, some hybrid of text-MeSH would probably be necessary.

Is the manually intensive approach to discovery for some of the techniques described in this paper cost-effective? We believe so. While having to sift through hundreds of thousands of phrases for the RP study sounds overwhelming, it is not a difficult process. For some categories, this sifting could be automated. For example, in the RP study, had we generated a list of foods, food derivatives, and other non-drug substances and lifestyle factors beforehand, we could have used it as a query to search for phrases, and eliminated a few weeks worth of labor. But even if automation were not possible in some cases, an extra few weeks for the phrase identification process will not add substantially to the cost of the total process. In the Cataracts, PD, and MS studies, we eliminated this step by using the MeSH defined non-drug semantic classes for potential solutions.

The final step of linking the Abstracts to the core literature is the time consuming step. But even here, suppose that an extra six man-months were required to read and evaluate the Abstracts. This might add another \$100K to the total study cost. The potential discovery could make major inroads on many chronic diseases in the medical field, and similar magnitude advances in the physical sciences. If we have truly found a path to discovery, these additional costs due to labor intensity are miniscule compared to the potential payoff. While we would prefer to eliminate these labor intensive costs if possible, we would rather incur these costs if the alternative is to use automation and lose most of the discovery. Paradoxically, it is the labor intensive discovery-enhancing approach that is cost-effective at present, not the automated discovery-eliminating approaches.

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## APPENDIX 1 – RAYNAUD’S PHENOMENON POTENTIAL DISCOVERIES

**TABLE 1 – POTENTIAL DISCOVERY CANDIDATES FOR TREATING RAYNAUD’S PHENOMENON (PARTIALLY VETTED)**

| DISCOVERY   | VAS         | AGG        | VIS        | EFFECT   |
|---|-------------|------------|------------|--|
| Bee Venom/ Melittin                                     | MED/<br>MED |            |            | Endothelium-dependent vasodilation by melittin (Forstermann and Neufang, 1985; Busse and Bassenge, 1985)   |
| Bony Fish/ Urotensin 1                                  | MED/<br>HI  |            |            | Selective dilation of the mesenteric vascular bed (MacCannell et al, 1980; Medakovic and Lederis, 1975.)   |
| Catfish   | MED/<br>MED | LO/<br>LO  |            | Catfish extracts ... induce a vasodilation similar to that of porcine VIP (Holder et al, 1983)   |
| Cod Liver Oil/ EPA/<br>DHA                              | MED/<br>MED | HI/<br>HI  |            | DHA .... inhibited aggregation of platelets .... Shift of the prostaglandin I/thromboxane A balance to a more antiaggregatory and vasodilatory state (Von Schacky et al, 1985)   |
| Fish Oil/ Salmon/<br>Menhaden/ EPA                      | MED/<br>MED | HI/<br>MED | HI/<br>MED | Augmentation of contractile effect of norepinephrine .... diminished by dietary intake of EPA (Lockette et al, 1982)   |
| Leech (Hirudin)   | MED/<br>HI  | MED/<br>HI |            | The experiments on effect of biting on host tissue give a faint indication of vascular dilation due to bite .... Leech secretion .... inhibits the ADP-induced aggregation of gel-filtered human platelets (Mishra and Dev, 1976)                                  |
| Salmon Calcitonin                                       | LO/<br>LO   |            |            | System ... metabolizes arachidonic acid to two biologically active oxygenated products; one of the products... relaxes blood vessels. Formation of ... oxygenated arachidonate metabolites is stimulated by ... salmon calcitonin (SCT) .(Schwartzman et al, 1985) |
| Agar-Agar   | HI/<br>MED  |            |            | The increased diameter (+ 35.78%) confirms the peripheral vasodilating theophylline effect (Cambar and Saurel, 1978)   |
|   |             |            |            |  |
| antihypertensive polar<br>renomedullary lipid<br>(APRL) | MED/<br>MED |            |            | Orally active vasodilators ..... decrease peripheral vascular resistance.... Provides direct evidence that APRL is a vasodilator with increased potency in SHR hypertension. (Smith et al, 1981; Muirhead et al, 1981)   |
| Fusaric Acid  | MED/<br>MED |            |            | Hypotension induced rapidly after intravenous administration of fusaric acid ... due to ... direct depression of cardiac function and decrease in peripheral vascular resistance (Furuta and Washizaki, 1976)  |
| Geranium  | MED/<br>MED | MED        |            | Analysis of the mechanism of the hypotensive action of geranium and of the   |

|                     |             |             |           |   |
|---------------------|-------------|-------------|-----------|---|
|                     |             |             |           | flavenoid fractions obtained indicated that this action results mainly from a direct effect on the vascular smooth muscles (Petkov, 1979)   |
| Enkephalins         | HI/<br>MED  |             |           | Intraarterially administered enkephalins exert a vasodilatory effect on vasculature in skeletal muscle which may be direct, indirect or both. (Moore and Dowling, 1982)   |
| Linoleic Acid       | HI/<br>MED  | MED/<br>MED |           | (PG) E1 which is a vasodilator ... PGE1 biosynthesis is enhanced by the essential fatty acid, linoleic acid .... A linoleic-acid-rich diet improved blood platelet aggregation (Horrobin, 1980; ten Hoor, 1980)   |
| Nitric Oxide        | MED/<br>MED | MED/<br>MED |           | Vascular smooth muscle relaxation elicited by nitrogen oxide-containing vasodilators. Nitrovasodilators are thought to form nitric oxide free radical and directly activate guanylate cyclase. ... S-nitrosothiols could serve as active intermediates in the inhibitory action of sodium nitroprusside, nitric oxide, and related nitrogen oxides on platelet aggregation (Gruetter et al, 1981; Rapoport and Murad, 1983; Mellion et al, 1981)  |
| Picolinic Acid      | MED/<br>MED |             |           | Hypotension induced rapidly after intravenous administration of ... picolinic acid ... due to ... direct depression of cardiac function and decrease in peripheral vascular resistance (Furuta and Washizaki, 1976)   |
| Benzoic Acid        | HI/<br>MED  | MED/<br>MED | HI/<br>HI | PG analog .... [(+)-4-(3-[3-[2-(1-hydroxycyclohexyl)-ethyl]-4-oxo-thiazolidinyl]-propyl) benzoic acid] ... is a potent arterial vasodilator. .... 2,3-Dihydroxybenzoic acid (2,3-DHB) inhibits the second wave of platelet aggregation .... The effect of hexobendine ... on the dynamic viscosity of blood-isotonic and hyperosmolal suspensions of human and rat erythrocytes .... caused a statistically significant reduction of viscosity (Siegl and Wenger, 1985; Seymour and Blaine, 1984; Greenberg et al, 1977; Winkler and Moser, 1983) |
| Coffee              | HI/<br>MED  |             |           | A coronary vasoconstrictor substance is present in regular and "decaffeinated" forms of both percolated and instant coffee. (Kalsne, 1977)  |
| Bed Rest            | MED/<br>MED |             |           | The beneficial results often credited to vasodilators in studies on congestive heart failure might in part be due to the concomitant bed rest introduced during the monitoring of the patients. (Thaulow et al, 1982)   |
| Reflexotherapy (RT) | MED/<br>MED |             |           | After RT was completed ..... the total peripheral vascular resistance dropped both at rest and after exercise. (Monaenkov et al,  |

|  |          |          |  |   |
|--|----------|----------|--|---|
|  |          |          |  | 1984)   |
| Wine/ grapes/ chocolate/ ingested hot water      | MED/ MED |          |  | Flushes provoked by the ingestion of water at 60 degrees C, red wine, and milk chocolate..... The active agent causing flushing in coffee at 60 degrees C is heat, not caffeine (Wilkin and Rountree, 1982; Wilkin, 1981)   |
| Coenzyme Q10                                     | MED/ MED |          |  | The mechanism of reduction of elevated blood pressures by CoQ10 is based upon normalization or autoregulation of peripheral resistance rather than cardiac regulation (Folkers et al, 1981)   |
| Hydration  | MED/ MED |          |  | The internal temperature (T <sub>es</sub> ) threshold for cutaneous vasodilation was elevated by 0.42 degree C in hypohydrated conditions; but once vasodilation occurred, the slope of the arm blood flow:T <sub>es</sub> relation was unchanged from control..... Vasopressin appears to have an important role as a vasoconstrictor agent whenever volume is threatened, such as in dehydration. (Nadel et al, 1980; Johnston, 1985) |
| Garlic   | MED/ MED | HI/ HI   |  | Addition of essential oil of garlic inhibited in-vitro platelet aggregation induced by ADP, epinephrine or collagen; the effect was dose-related .... Hypotensive action of garlic ..... is a matter mainly of cholinomimetic and to a less extent of vascular smooth-muscle effects (Bordia, 1978; Petkov, 1979)   |
| Margarine/ trans-trans linoleic acid (avoidance) | MED/ MED | MED/ MED |  | Introduction of a new, unnatural dietary fatty acid--trans-trans linoleic acid--in margarine ..... caused vasoconstriction while the clumping of platelets was greatly increased (Martin, 1983, 1984)   |
| Mistletoe (Viscum Albin)                         | MED/ MED |          |  | Aqueous extracts of mistletoe exercise a hypotensive effect mainly of cholinomimetic character (Petkov, 1979)   |
| Mushroom   | MED/ MED |          |  | Mushroom Tricholoma conglobatum. .... effects on the kallikrein-kinin system (MH - Vasodilator Agents) (Kizuki et al, 1979)   |
| Natto fermented soy                              | MED/ MED |          |  | Relationship between natto-added feed and blood pressure (Hiyashi, 1976)  |
| Olive Leaves (oleuropein)                        | MED/ MED |          |  | Oleuropein .... Coronarodilating action .... Increased coronary flow by 63% (Petkov, 1979)  |
| Scopoletin                                       | MED/ MED |          |  | 4-metilesculetin antagonizes the contraction induced by 5-HT probably through activation of the synthesis of vasodilator prostaglandins (MH - Scopoletin/*pharmacology) (Bettini et al, 1979)   |
| Tetrahydroxystilbene                             | MED/ MED |          |  | The coronary vasodilatory ..... effects of 3,3',4,5'-tetrahydroxystilbene and its derivatives (Inamori et al, 1984)   |
| Forskolin  | MED/     |          |  | Coronary vasodilator potency of forskolin.  |

|   |             |  |  |  |
|---|-------------|--|--|--|
|   | MED         |  |  | Forskolin consistently induced concentration-dependent ..... decreases in coronary vascular resistance (Vaden and Adams, 1985)   |
| leaves of <i>Callicarpa dichotoma</i>                               | MED/<br>MED |  |  | Leaves of <i>Callicarpa dichotoma</i> ..... MH - Vasodilator Agents (Liu, 1983)  |
| Dihydropyranocoumarins / dihydrofuranocoumarins                     | MED/<br>MED |  |  | For certain esters of dihydropyranocoumarin- and dihydrofuranocoumarin alcohols coronary vasodilatory ..... activities comparable to those of papaverine were observed (Thastrup et al, 1983)  |
| Dehydroevodiamine from <i>Evodiae Fructus</i>                       | MED/<br>MED |  |  | Dehydroevodiamine isolated from <i>Evodiae Fructus</i> lowered blood pressure ..... implying a vasodilatory effect (Xu et al, 1982)  |
| Huang Chin extract ( <i>Scutellaria baicalensis</i> George)         | MED/<br>MED |  |  | Huang Chin extract produces peripheral vasodilatation which leads to a hypothermia in conscious rats (Lin et al, 1980)   |
| Sinomenine  | MED/<br>MED |  |  | The released histamine is responsible for the dominant pharmacological actions of sinomenine, such as vasodilatation, increased vascular permeability (Yamasaki, 1976)   |
| Buphenin  | MED/<br>MED |  |  | The vasodilator .....buphenin ..... stimulated the spontaneous phasic activity of ..... isolated rat portal vein preparations (Michailov et al, 1979)  |
| Crataemon (flavonoid mixture of <i>Crataegus monogyna</i> )         | MED/<br>MED |  |  | Crataemon increases dog coronary blood flow .... increased the coronary flow of isolated rabbit heart by 162% ..... general peripheral resistance is much less inhibited ..... rather promising coronarodilating drug (Petkov, 1979; Taskov, 1977) |
| Peucordin (sum of furocoumarines from <i>Peucedanum arenarium</i> ) | MED/<br>MED |  |  | Peucordin (sum of furocoumarines from <i>Peucedanum arenarium</i> ) increased coronary flow of isolated rabbit heart by more than 165% ..... coronarodilating effect is analogous to ..... Crataemon (Petkov, 1979)                                |
| Prenylamine   | MED/<br>MED |  |  | Prenylamine and carbochromen dilated preferentially the small arteries (Kamitani et al, 1977)  |
| Puerarin  | MED/<br>MED |  |  | The effect of intravenous puerarin on acute myocardial infarction (MH - Vasodilator Agents/therapeutic use) (Li et al, 1985)   |
| Tetramethylpyrazine   | MED/<br>MED |  |  | Tetramethylpyrazine ..... caused prominent systemic and coronary vasodilation (Dai and Bache, 1985)  |
| Valerian Root Extracts  | MED/<br>MED |  |  | One of the valepotriatic fractions [from the valerian roots] ... is characterized .... by coronarodilating ..... Action (Petkov, 1979)   |
| Platycodin  | MED/<br>MED |  |  | Vasodilating effect of crude platycodin in anesthetized dogs (Kato et al, 1973)  |
| Acetazolamide   | MED/<br>MED |  |  | Acetazolamide nevertheless caused a rapid vasodilation in the brain ..... We suggest that this agent has a local vasodilator effect on the cerebral arterioles (Hauge et al, 1983)   |

|  |             |             |  |  |
|--|-------------|-------------|--|--|
| Testosterone                           | MED/<br>MED |             |  | The largest significant increases in diameter [ovarian and uterine veins], particularly after 21 days, were observed in mice treated with testosterone (Forbes and Glassen, 1972)  |
| Malva rotundifolia                     | MED/<br>MED |             |  | Malva rotundifolia, a potential vasodilator (Kratzer and Greif, 1969)  |
| APRL                                   | MED/<br>MED |             |  | The alkyl ether analogs of phosphatidylcholine (..... APRL) are orally active vasodilators. They cause a prolonged depressor effect due to a decrease in peripheral vascular resistance (Muirhead et al, 1981)   |
| Atrial Natriuretic Polypeptide/ Factor | MED/<br>MED |             |  | Alpha-hANP .... resulted in a rapid and marked fall of .... total peripheral resistance .... decreased vascular resistance in most organs .... related to a vasodilator action (Fujioka et al, 1985; Winquist et al, 1985)   |
| Vinca species                          | MED/<br>MED |             |  | Brovincamine produces a vasodilation .... the total alkaloid sum of Vinca herbacea .... produces a continuous decrease of blood pressure ... Central, ganglioblocking and peripheral vascular mechanisms underlie this hypotensive action (Katsuragi et al, 1984; Petkov, 1979)                    |
| Fumitory (protopin)                    | MED/<br>MED |             |  | Protopin .... a marked vasodilating effect was observed on the blood vessels of isolated rabbit ear (Petkov, 1979)   |
| Astragalus                             | MED/<br>MED |             |  | A positive property of Astragalus is the combination of its hypotensive effect with .... a coronarodilating action. .... Some of the other effects of different Astragalus subspecies such as vasodilating .... Might also be explained by the presence of gamma-aminobutyric acid. (Petkov, 1979) |
| Hydroxylamine                          | MED/<br>MED |             |  | A series of beta-hydroxylamine-phenylpropyl hydroxamic acids .... can be classified as direct acting vasodilators (Kehl et al, 1978)   |
| Molsidomine                            | MED/<br>MED |             |  | Molsidomine is a venous vasodilator with useful pharmacokinetic properties (Witchitz et al, 1981)  |
| Doxepin                                | MED/<br>MED |             |  | The vasodilator activity of doxepin was probably a manifestation of the smooth muscle spasmolytic properties of the drug (Constantine et al, 1964)   |
| Lidoflazine                            | MED/<br>MED |             |  | Lidoflazine .... block calcium fluxes .... in the peripheral vessels (Singh et al, 1985).  |
| Streptidin                             | MED/<br>MED |             |  | The relaxant and antispasmodic effects of streptidin on smooth muscles (Altinkurt, 1970)   |
| Viquidi                                | MED/<br>MED | MED/<br>MED |  | The antithrombotic activity of viquidil, a cerebral vasodilator (Sim and Uzan, 1979)   |
| Ethaverine                             | MED/<br>MED |             |  | Ethaverine provoked an appropriate redistribution ... selectivity of coronary dilator action on large or small vessels   |

|   |             |             |  |   |
|---|-------------|-------------|--|---|
|   |             |             |  | (LaCroix et al, 1978)   |
| Dilazep   | MED/<br>MED |             |  | Dilazep .... dilated the vessel (Suzuki et al, 1984)  |
| Ethyl apovincamate  | MED/<br>MED |             |  | Vasodilating effect of ethyl apovincamate on conjunctival vessels (Brooser et al, 1976)   |
| Gamma-aminobutyric acid (GABA)                              | MED/<br>MED |             |  | GABA increases total cerebral blood flow .... vasodilation induced by GABA .... effects of different Astragalus subspecies such as vasodilating .... might also be explained by the presence of gamma-aminobutyric acid (Alborch et al, 1984; Petkov, 1979) |
| Bupicomide  | MED/<br>MED |             |  | Bupicomide .... is acting as a direct vasodilator (Velasco et al, 1975)   |
| Fusaric Acid [picolinic acid derivative] and Picolinin Acid | MED/<br>MED |             |  | Hypotension induced rapidly after intravenous administration of fusaric acid or 5-(4'-chlorobutyl) picolinic acid is .... due to .... decrease in peripheral vascular resistance (Furuta and Washizaki, 1976)   |
| Secretin  | MED/<br>MED |             |  | Secretin produced similar vasodilation in all organs .... duodenum, jejunum, heart, kidney, forelimb, spleen, and the skin and muscle of the forelimb (Chou et al, 1977; Fara, 1975; Richardson and Withrington, 1976)                                      |
| Cetiedil  | MED/<br>MED |             |  | Cetiedil .... brings about peripheral vasodilation (Boissier et al, 1978)   |
| Etafenone   | MED/<br>MED | MED/<br>MED |  | Etafenone, a new coronary vasodilator with antiarrhythmic properties .... Inhibitory effect of etafenone hydrochloride on platelet aggregation (Hashimoto et al, 1979; Ujiie et al, 1983)   |
| N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide          | MED/<br>MED |             |  | N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide .... produces relaxation of isolated vascular strips (Hidaka et al, 1978)  |
| 2-nicotinamidoethyl nitrate                                 | MED/<br>MED |             |  | In vivo, .... 2-nicotinamidoethyl nitrate .... may have a more potent vasodilating action (Inoue et al, 1984)   |
| Phyllanthus   | MED/<br>MED |             |  | A non-competitive antagonism of noradrenaline-induced contractions by the Phyllanthus sellowianus alkaloid was also demonstrated on aortic rings (Calixto et al, 1984)  |
| Caroverine fumarate   | MED/<br>MED |             |  | Vasorelaxant action of caroverine fumarate (Ishida et al, 1980)   |
| Malva rotundifolia (Dwarf Mallow)                           | MED/<br>MED |             |  | Malva rotundifolia, a potential vasodilator (Kratzer and Greif, 1969)   |
| Shan-dou-gen  | MED/<br>MED |             |  | The hypothermia in response to Shan-dou-gen was brought about by .... cutaneous vasodilatation (Lin et al, 1980)  |
| Oliverine   | MED/<br>MED |             |  | Oliverine .... has an antihypertensive effect .... hypotensive by a relaxant close to papaverine action on vascular smooth muscles (Quevauviller and Hamonniere,  |



|   |             |             |  |  |
|---|-------------|-------------|--|--|
|   |             |             |  | 1977)  |
| Sinomenine                                    | MED/<br>MED |             |  | Sinomenine .... releases histamine .... responsible for the dominant pharmacological actions of sinomenine, such as vasodilatation, increased vascular permeability (Yamasaki, 1976)   |
| Beta-Endorphin                                | MED/<br>MED |             |  | Beta-Endorphin .... dilated in vivo the arteriole of the microcirculatory system in hamster cheek pouch (Wong et al, 1981).  |
| Mebeverine                                    | MED/<br>MED |             |  | Mebeverine bound to beta 2- and alpha-receptors and inhibited phosphodiesterase activity (Greenslade et al, 1982)  |
| Ethyl Flavone-7-Oxyacetate                    | MED/<br>MED |             |  | Pharmacological and Toxicological Study of a Coronary Vasodilator: Ethyl Flavone-7-Oxyacetate (Morin et al, 1964)  |
|   |             |             |  |  |
|   |             |             |  |  |
| Butter  |             | MED/<br>MED |  | Feeding 75 g of butter to healthy males .... enhanced the tendency of platelet adhesiveness and platelet aggregation to a significant level (Bordia and Verma, 1985).  |
| Cis-unsaturated fatty acids                   |             | MED/<br>MED |  | All the cis-unsaturated fatty acids tested inhibited aggregation (Kitagawa et al, 1985; MacIntyre et al, 1984)   |
| Heated Fats                                   |             | MED/<br>MED |  | A semisynthetic diet containing .... a mixture of polyunsaturated oils subjected to heating and characterized by elevated indexes of thermal alteration .... resulted in ....elevation of platelet thromboxane formation and decrease of vascular prostacyclin release (Giani et al, 1985) |
| Peanuts (fresh)                               |             | MED/<br>MED |  | Platelet aggregation and stickiness has also been found to be decreased by the use of peanuts (Vazquez et al, 1982)  |
| Saturated Fatty Acids                         |             | MED/<br>MED |  | Inhibition of ADP-induced aggregation of bovine platelets by saturated fatty acids (Kitagawa et al, 1984)  |
| Mussel Broth                                  |             | MED/<br>MED |  | Sulphated polysaccharide (S-Lim) .... isolated from mussel broth .... displayed an anticoagulant activity .... found to inhibit thrombin-induced platelet aggregation (Nilsson et al, 1982)  |
| Dihomogammalinolenic acid                     |             | MED/<br>MED |  | Dihomogammalinolenic acid (20:3 omega 6) is more anti-aggregatory than eicosapentaenoic (20:5 omega 3) in a platelet-endothelial cell mixture  |
| Carrageenan                                   |             | MED/<br>MED |  | All four carrageenans caused some precipitation of plasma proteins, and induced aggregation in platelet-rich plasma or washed platelet suspensions (McMillan et al, 1979)  |
| Tan-Shen (radix of Salvia miltiorrhiza Bunge) |             | MED/<br>MED |  | New platelet aggregation inhibitors from Tan-Shen (Onitsuka et al, 1983)   |
| N-acetylcysteine                              | MED/<br>MED | HI/<br>HI   |  | N-acetylcysteine potentiated markedly the inhibitory effect of nitroglycerin on platelet   |

|                               |             |             |  |   |
|-------------------------------|-------------|-------------|--|---|
|                               |             |             |  | aggregation .... NAC [N-acetylcysteine] potentiates the vasodilator effects of NTG [nitroglycerin] in man (Loscalzo, 1985; Horowitz et al, 1983)  |
| flavin adenine dinucleotide   |             | MED/<br>MED |  | Flavin adenine dinucleotide .... could inhibit H <sub>2</sub> O <sub>2</sub> -induced platelet aggregation .... Flavine adenine dinucleotide (FAD) may inhibit not only the aggregation but also ATP release of platelets in vitro (Higashi et al, 1978; Shimada et al, 1983)   |
| Auranofin                     |             | MED/<br>MED |  | Auranofin .... was found to be a potent inhibitor of ADP-, epinephrine-, or collagen-induced platelet aggregation (Nathan et al, 1983)  |
| Injectio Salvia Miltiorrhizae |             | MED/<br>MED |  | Injectio Salvia Miltiorrhizae .... inhibited platelet aggregation and serotonin release induced by either ADP or epinephrine in a dose dependent manner (Wang et al, 1982)  |
| Quercetin                     | LO/<br>LO   | MED/<br>MED |  | Quercetin .... inhibit washed human platelet aggregation and secretion of serotonin induced by ADP, collagen or thrombin (Beretz et al, 1982)   |
| Fendiline                     | MED/<br>MED |             |  | Fendiline dose dependently increased coronary flow by up to 200% .... The counteraction of the "washout effect" by fendiline .... is most likely due to the opening of additional (previously closed) capillaries (Kukovetz et al, 1976)  |
| Dantrolene                    | MED/<br>MED |             |  | Dantrolene blocks intracellular calcium release in smooth muscle: competitive antagonism of thromboxane A <sub>2</sub> (Ally et al, 1978)   |
| Oxybutynin                    | MED/<br>MED |             |  | Oxybutynin has a vasodilating action probably ascribable to its anticholinergic and antispasmodic actions (Misawa et al, 1984)  |
| Gingvoree                     | MED/<br>MED |             |  | A vasodilator agent from the leaves of the gingvoree (Fischer, 1967)  |
| Auricularia auricula          |             | MED/<br>MED |  | Inhibition of human and rat platelet aggregation by extracts of Mo-er (Auricularia auricula) (Agarwal et al, 1982)  |
| Coffee Extracts               |             | MED/<br>MED |  | Coffee extracts contain compounds which are active in inhibiting platelet aggregation????   |
| Melatonin                     |             | MED/<br>MED |  | Collagen-induced platelet aggregation ... is inhibited ... by preincubation of gel-filtered platelets with melatonin (Leach and Thorburn, 1980).  |
| Nucleic Acids                 |             | MED/<br>MED |  | If human platelets react to uric acid in the same manner as rat platelets this might explain the link that has been suggested between hyperuricaemia and ischaemic heart disease. In that event diets high in nucleic acids might be contra-indicated in people at risk from ischaemic heart disease (Winocour et al, 1978) |

|                             |  |             |             |  |
|-----------------------------|--|-------------|-------------|--|
| Catechin                    |  | MED/<br>MED |             | Anti-platelet aggregation effect of d-catechin (He, 1982)  |
| Selenium                    |  | MED/<br>MED |             | The effect of selenium supplementation on in vivo platelet aggregability was studied by measuring plasma levels of beta-thromboglobulin and platelet factor 4, two proteins secreted concomitant with aggregation. beta-thromboglobulin diminished 7.5 +/- 11.0 ng/ml and platelet factor 7.6 +/- 11.0 ng/ml during selenium supplementation .... The aggravation in selenium deficient mice may be due to enhanced platelet aggregation (Stead et al, 1985; Masukawa et al, 1983) |
| Sucrose                     |  | MED/<br>MED |             | In animals maintained on a semisynthetic diet containing sucrose (62%) as the only carbohydrate source, platelet adhesiveness increased as compared with that in rats fed a normal chow pellet. (Suzuki, 1975)   |
| Citric                      |  | MED/<br>MED |             | The effect of ascorbic acid (A.A.) was compared to that of HCl and citric acid (C.A.). ADP- and collagen-induced aggregation of normal platelets were significantly impaired by both A.A. and C.A. .... Citrate appears to inhibit aggregation as well as MDA synthesis. (Cowan et al, 1975; Huijgens et al, 1983)   |
| Vernolepin/ Dried Fruit     |  | HI/<br>HI   |             | The first pharmacological characterization of vernolepin revealed ... an antiaggregating and disaggregating activity against rabbit platelet aggregation induced by arachidonic acid (Laekeman et al, 1983)  |
| Bromelain/ Pineapple        |  | HI/<br>HI   |             | Bromelain therapy leads to formation of platelets with increased resistance to aggregation (Felton, 1980)  |
| Soybean Phosphatidylcholine |  | MED/<br>MED | MED/<br>MED | The [cholesterol] lowering was accompanied by a reduction in membrane microviscosity .... and a decrease in the rate of the ADP- and collagen-induced platelet aggregation (Borodin et al, 1985)   |
| Onion                       |  | MED/<br>MED |             | Aqueous extracts of onion, garlic and ginger inhibited platelet aggregation induced by several aggregation agents, including arachidonate (AA), in a dose-dependent manner. .... observed antiplatelet activity of onion relates to the presence of a non-polar, heat stable inhibitor of thromboxane synthesis (Srivastava, 1984; Makheja et al, 1979)  |
| Ginger                      |  |             |             | Aqueous extracts of onion, garlic and ginger inhibited platelet aggregation induced by several aggregation agents, including arachidonate (AA), in a dose-dependent manner. (Srivastava, 1984)   |
| Artichoke                   |  | MED/        |             | The platelets ability to aggregate, whether  |

|  |  |             |       |   |
|--|--|-------------|-------|---|
|  |  | MED         |       | spontaneously or by induction was found to be statistically significantly reduced [by an artichoke extract as a preparation called Cynarex] (Woyke et al, 1981)   |
| Canbra Oil   |  | MED/<br>MED |       | In vitro platelet aggregation by ADP dropped significantly in subjects fed the canbra oil diet. (Jacotot et al, 1978)   |
| Moutan Cortex  |  | HI/<br>HI   |       | One week oral administration of water extract of Moutan Cortex [Moutan Cortex (w), 3 g/day] significantly reduced platelet aggregation and thromboxane B2 (TXB2) formation induced by collagen, epinephrine and ADP. (Hirai et al, 1983)  |
| Fungi<br>(see also Mushroom<br>above for vasodilation) |  | MED/<br>MED |       | Low dalton compounds from aqueous dialysates of several edible fungi have demonstrated inhibition of platelet aggregation in vitro. The species of fungi included Auricularia polytricha (black tree fungus), Cortinellus shiitake (shiitake mushroom), Agaricus biporus, and Auriculariaceae sp. (white tree fungus). (Hokama and Hokama, 1981)  |
| CARBOXYLIC ACID<br>(Binifibrate)                       |  |             | HI/HI | Binifibrate increased passage of a suspension of red blood cells at 80% haematocrit value through filters of 30-40 micron (Teitel's method), and erythrocyte deformability detectable by increase of flow rate through filters of pore size lesser than erythrocyte diameter (Schmid-Schonbein's method). (Bruseghini et al, 1983)  |
| Ruscogenin   |  | MED/<br>MED |       | In patients with postthrombotic syndrome the medium blood stream velocity in the V. femoralis increased on the diseased side two hours after oral application of a high-dosed combination of ruscogenin, ... (Marshall, 1984)   |
| Placenta   |  | MED/<br>MED |       | The placenta contains .... some antithrombotic factors, for example, placental plasminogen activator and platelet aggregation inhibitor (Shidara, 1984)   |
| Ticks  |  | MED/<br>MED |       | Platelet antiaggregating activity in the salivary secretion of the blood sucking bug Rhodnius prolixus. .... Saliva of mosquitoes .... inhibits the ADP- and collagen-mediated aggregation of platelets. .... Pilocarpine-induced saliva of the tick, Ixodes dammini, inhibited platelet aggregation triggered by ADP and collagen, as well as platelet-aggregation factor (Rebeiro and Garcia, 1981; Rebeiro et al, 1984; Rebeiro et al, 1985) |
| Sodium Azide   |  | MED/<br>MED |       | Sodium azide in low concentrations (0.1-10 micrometer) was found to have inhibitory effects on human platelet function. Primary aggregation induced by ADP, epinephrine,  |

|                               |             |             |             |   |
|-------------------------------|-------------|-------------|-------------|---|
|                               |             |             |             | thrombin and the ionophore A 23187 was decreased. (Stibbe and Holmsen, 1977)  |
| Huang Chin                    | MED/<br>MED |             |             | The hypothermia in response to Huang Chin application was brought about solely by cutaneous vasodilatation (lin et al, 1980)  |
| Sulphated Polysaccharide      |             | MED/<br>MED |             | The sulphated polysaccharide (S-Lim) displayed an anticoagulant activity in a thrombin test system with human plasma (Nilsson et al, 1982)  |
| Melon                         |             | MED/<br>MED |             | An active fraction was isolated from an aqueous melon extract (Cucurbitacea cucumis melo) and was shown that it inhibits human platelet aggregation induced by epinephrine, ADP, collagen, thrombin, sodium arachidonate, prostaglandin endoperoxide analogue U-46619 and PAF-acether (Altman et al, 1985)  |
| Phenolic Compounds            |             | MED/<br>MED |             | Inhibition of arachidonate induced platelet aggregation was examined for three of the more potent inhibitors. 2-Benzoyloxyphenol and 2,4,6-trimethylphenol were more potent than indomethacin when assayed using a 2 min preincubation of inhibitor with platelets  |
| Egg Yolk                      |             |             | MED/<br>MED | In vivo treatment of morphine-addicted mice with AL ... [lipid mixture extracted from hen egg-yolk (Active-lipid, AL)] ... reversed the brain membrane hyperviscosity (Heron et al, 1982)   |
| Fasting                       |             | HI/<br>MED  | HI/<br>MED  | Fasting was discovered to lead to the reduction of blood plasma and red cell coagulation, to the deterioration of platelet aggregation, rise in the oxidized hemoglobin content, and to the increase in red cell resistance to peroxide hemolysis.(Muliar et al, 1984)  |
| Cocoa Butter                  |             |             | MED/<br>MED | VLDL and LDL were more fluid from rabbits fed cocoa butter than from rabbits fed corn oil (Berlin and Young, 1980)  |
| Guar Gum                      |             |             | MED/<br>MED | .... guar gum for 4 weeks. They experienced a decrease in (1) plasma fibrinogen, (2) insulin requirement, (3) serum osmolality and (4) plasma viscosity; and an increase in serum albumin and total serum protein concentrations. The decrease in plasma viscosity, which was statistically significant (Koepp and Hegewisch, 1981.)  |
| Drag Reducing Polymers (Okra) |             |             | HI/<br>HI   | Under appropriate conditions of flow, however, the addition of linear polymers of high mol. wt--of the order of 10(5) to 10(7) daltons--may cause the flow to increase as much as 3-fold and occasionally more without altering the driving pressure..... A marked fall in the pressure gradients of constant blood flows through pipes has also been observed upon the addition of |

|  |  |             |           |   |
|--|--|-------------|-----------|---|
|  |  |             |           | polyacrylamide, poly(ethylene oxide), deoxyribonucleic acid, or a polysaccharide extracted from okra. (Polimeni et al, 1985)  |
| Cell Hydration/<br>Hydration/Dehydration/<br>Hypohydration |  |             | HI/<br>HI | Optimal rheologic behavior was exhibited by normal RBC when their water content was in the normal range. A rise or a fall in cell hydration resulted in a decrease in cell deformability ..... Maximal arm blood flow was reduced by nearly 50% in hypohydration. (Gulley et al, 1982; Nadel et al, 1980) |
| Feverfew   |  | MED/<br>MED |           | Extracts of feverfew ( <i>Tanacetum parthenium</i> ) inhibited secretory activity in blood platelets ..... Platelet aggregation was consistently inhibited (Heptinstall et al, 1985)  |
| Tricholysine (lower fungi)                                 |  | MED/<br>MED |           | Tricholysine (triale) and longolytin, isolated from cultural fluid of two similar lower fungi <i>Trichothecium roseum</i> and <i>Arthrobotrys longa</i> , exhibited anticoagulant and fibrinolytic properties after addition to blood plasma of experimental animals. (Serebriakova et al, 1984)          |

## REFERENCES for Appendix 1

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Monaenkov AM, Lebedeva OD, Demina IF. [Use of graded bicycle ergometry as a method for the objective evaluation of the efficacy of reflexotherapy in the early stages of hypertension] *Ter Arkh*. 1984;56(9):34-6.

37. "Flushes provoked by the ingestion of water at 60 degrees C, red wine, and milk chocolate."

Wilkin JK, Rountree CB. Blockade of carcinoid flush with cimetidine and clonidine. *Arch Dermatol*. 1982 Feb;118(2):109-11.

38. "Both coffee at 60 degrees C and water at 60 degrees C led to flushing reactions with similar temporal characteristics and of similar intensities. It is concluded that the active agent causing flushing in coffee at 60 degrees C is heat, not caffeine"

Wilkin JK. Oral thermal-induced flushing in erythematotelangiectatic rosacea. *J Invest Dermatol.* 1981 Jan;76(1):15-8.

39. "A greater deficiency of CoQ10 in the vascular system than in blood is likely. We consider that (1) the mechanism of reduction of elevated blood pressures by CoQ10 is based upon normalization or autoregulation of peripheral resistance rather than cardiac regulation, and (2) that the therapeutic activity of CoQ10 is not pharmacodynamic, but results from a translational increase in levels of CoQ10-enzymes in vascular tissue during ca. 4-12 weeks."

Folkers K; Drzewoski J; Richardson PC; Ellis J; Shizukuishi S; Baker L. Bioenergetics in clinical medicine. XVI. Reduction of hypertension in patients by therapy with coenzyme Q10. *Res Commun Chem Pathol Pharmacol (United States)* Jan 1981, 31 (1) p129-40

40. "Hypohydration resulted in a significantly reduced cardiac output during exercise; this the result of a reduction in stroke volume of 17 ml.beat-1 without adequate elevation in heart rate. the internal temperature (T<sub>es</sub>) threshold for cutaneous vasodilation was elevated by 0.42 degree C in hypohydrated conditions; but once vasodilation occurred, the slope of the arm blood flow:T<sub>es</sub> relation was unchanged from control. Maximal arm blood flow was reduced by nearly 50% in hypohydration"

Nadel ER, Fortney SM, Wenger CB. Effect of hydration state of circulatory and thermal regulations. *J Appl Physiol.* 1980 Oct;49(4):715-21.

41. "Vasopressin appears to have an important role as a vasoconstrictor agent whenever volume is threatened, such as in dehydration, haemorrhage, adrenal insufficiency and orthostasis. It seems unlikely that vasopressin acts as a direct vasoconstrictor agent in the pathogenesis of any form of experimental or human hypertension."

Johnston CI. Vasopressin in circulatory control and hypertension. *J Hypertens.* 1985 Dec;3(6):557-69.

42. "Pharmacological analysis of the hypotensive action of garlic and of the purified fractions obtained by it pointed out that it is a matter mainly of cholinomimetic and to a less extent of vascular smooth-muscle effects"

Petkov, V. Plants and hypotensive, antiatheromatous and coronarodilatating action. *Am J Chin Med.* 1979 Autumn;7(3):197-236.

43. “The unnatural trans-trans isomer of linoleic acid, which had never been in human food prior to 1920 and which entered our food in margarines and refined oils, blocked the conversion of natural cis-cis linoleic acid to prostaglandin E1, which tends to prevent MI, both by acting as a vasodilator and by minimizing platelet aggregation.”

Martin W. The beriberi analogy to myocardial infarction. *Med Hypotheses.* 1983 Feb;10(2):185-98.

44. “It is suggested that MI is largely caused by coronary blood clots formed at the site of a break in the coronary artery endothelium; that the introduction of a new, unnatural dietary fatty acid--trans-trans linoleic acid--in margarine and refined vegetable oils in the 1920s, by inducing a deficiency of beneficial prostaglandin E1 (PGE1) while greatly increasing harmful thromboxane A2 (TXA2), caused vasoconstriction while the clumping of platelets was greatly increased”

Martin W. The combined role of atheroma, cholesterol, platelets, the endothelium and fibrin in heart attacks and strokes. *Med Hypotheses.* 1984 Nov;15(3):305-22.

45. “Aqueous extracts of mistletoe exercise a hypotensive effect mainly of cholinomimetic character.”

Petkov, V. Plants and hypotensive, antiatheromatous and coronarodilatating action. *Am J Chin Med.* 1979 Autumn;7(3):197-236.

46. “Kinin-inactivating enzyme from the mushroom *Tricholoma conglobatum*. IV. Its effects on the kallikrein-kinin system.”

Kizuki K, Moriya H, Moriwaki C. Kinin-inactivating enzyme from the mushroom *Tricholoma conglobatum*. IV. Its effects on the kallikrein-kinin system. *Chem Pharm Bull (Tokyo).* 1979 Jul;27(7):1618-25.

47. “Substances capable of reducing the blood pressure existed in ethanol extracts of dead *Bacillus natto*”

Hayashi U, Nagao K. Relationship between natto-added feed and blood pressure of SHR: experiment in feeding of propagation type natto *Bacilli*. *Jpn Heart J.* 1978 Jul;19(4):617.

48. "Platelet aggregation and stickiness has also been found to be decreased by the use of peanuts. The peanuts should be quite fresh, however, as two and three year old peanuts can become very rancid and cause actual damage to the blood vessels. (Ref. Revista Clinica Espanola 165(2): 85-89; April 30,1982)"

Salvador Vazquez M, Martinez Manzanares C, Constantino Bermejo M, Romero Velasco E. [Effect of a diet supplemented with unsaturated fatty acids (*Arachis hypogaea*: peanuts) on blood coagulation]. Rev Clin Esp. 1982 Apr 30;165(2):85-9.

49. "[The coronary vasodilatory and hypotensive effects of 3,3',4,5'-tetrahydroxystilbene and its derivatives]"

Inamori Y, Kubo M, Kato Y, Yasuda M, Baba K, Kozawa M. [The coronary vasodilatory and hypotensive effects of 3,3',4,5'-tetrahydroxystilbene and its derivatives]. Yakugaku Zasshi. 1984 Jul;104(7):819-21.

50. "Coronary vasodilator potency of forskolin. Forskolin consistently induced concentration-dependent ..... decreases in coronary vascular resistance".

Vaden SL, Adams HR. Inotropic, chronotropic and coronary vasodilator potency of forskolin. Eur J Pharmacol. 1985 Nov 26;118(1-2):131-7.

51. "Leaves of *Callicarpa dichotoma* ..... MH - Vasodilator Agents"

Liu WX. [Pharmacological studies on the leaves of *Callicarpa dichotoma*]. Zhong Yao Tong Bao. 1983 Nov;8(6):33-5.

52. "For certain esters of dihydropyrancoumarin- and dihydrofuranocoumarin alcohols coronary vasodilatory and spasmolytic activities comparable to those of papaverine were observed"

Thastrup O, Fjalland B, Lemmich J. Coronary vasodilatory, spasmolytic and cAMP-phosphodiesterase inhibitory properties of dihydropyrancoumarins and dihydrofuranocoumarins. Acta Pharmacol Toxicol (Copenh). 1983 Apr;52(4):246-53.

53. "Dehydroevodiamine isolated from *Evodiae Fructus* lowered blood pressure with bradycardia in anesthetised rats. At a cumulative dose of 22.5mg/kg/30min, there was a very significant decrease in blood pressure and heart rate. There was a more important decrease in diastolic pressure than systolic pressure, implying a vasodilatory effect".



Xu SB, Huang YM, Lau CN, Wat CK, Kong YC. Hypotensive effect of dehydroevodiamine from *Evodiae Fructus*. *Am J Chin Med*. 1982;10(1-4):75-85.

54. "The data indicate that Huang Chin extract produces peripheral vasodilatation which leads to a hypothermia in conscious rats."

Lin MT, Liu GG, Wu WL, Chern YF. Effects of Chinese herb, Huang Chin (*Scutellaria baicalensis* George) on thermoregulation in rats. *Jpn J Pharmacol*. 1980 Feb;30(1):59-64.

55. "The released histamine is responsible for the dominant pharmacological actions of sinomenine, such as vasodilatation, increased vascular permeability, acceleration of the thoracic and peripheral lymph flow, contraction of plain muscles, increased peristalsis of the intestines, and stimulation of gastric acid secretion."

Yamasaki H. Pharmacology of sinomenine, an anti-rheumatic alkaloid from *Sinomenium acutum*. *Acta Med Okayama*. 1976 Feb;30(1):1-20.

56. "The vasodilator and tocolytic substance buphenin (10  $\mu$ mol/l) stimulated the spontaneous phasic activity of some (8 out of 18) isolated rat portal vein preparations ..... buphenin exerts dual action upon rat portal vein: the drug partially stimulates the beta-receptors and partially blocks the alpha-adrenergic receptors."

Michailov MC, Felix W, Welscher U. Effects of buphenin on the rat portal vein. *Indian J Physiol Pharmacol*. 1979 Oct-Dec;23(4):254-60.

57. 'Crataemon (flavenoid sum obtained from the blossoms and leaves of *Crataegus monogyna*) ..... increased the coronary flow of isolated rabbit heart by 162% ..... rather promising coronarodilating drugs'

Petkov, V. Plants and hypotensive, antiatheromatous and coronarodilatating action. *Am J Chin Med*. 1979 Autumn;7(3):197-236.

58. 'Crataemon increases dog coronary blood flow .... general peripheral resistance is much less inhibited'

Taskov M. On the coronary and cardiotonic action of crataemon. *Acta Physiol Pharmacol Bulg*. 1977;3(4):53-7.

59. 'Peucordin (sum of furocoumarines from *Peucedanum arenarium*) increased coronary flow of isolated rabbit heart by more than 165% ..... coronarodilating effect is analogous to ..... Crataemon'.

Petkov, V. Plants and hypotensive, antiatheromatous and coronarodilatating action. *Am J Chin Med.* 1979 Autumn;7(3):197-236.

60. "Nitrate vasodilators relaxed selectively the large arteries, while adenosine, prenylamine and carbochromen dilated preferentially the small arteries."

Kamitani T, Nakano K, Mori J, Katsuki S, Honda F. Local specificity in responses of canine coronary vessels to oxygen deficiency and antianginal drugs. *Arch Int Pharmacodyn Ther.* 1977 Feb;225(2):257-74.

61. "Hypotensive effect of oleuropein ..... due to both central and peripheral actions ..... All these results point to the iridoid oleuropein isolated from olive leaves as a promising antihypertensive, coronarodilating and antiarrhythmic drug".

Petkov, V. Plants and hypotensive, antiatheromatous and coronarodilatating action. *Am J Chin Med.* 1979 Autumn;7(3):197-236.

62. "The effect of intravenous puerarin on acute myocardial infarction"  
Li XY, Wang PR, Shao JH. [The effect of intravenous puerarin on acute myocardial infarction] *Zhonghua Xin Xue Guan Bing Za Zhi.* 1985 Sep;13(3):175-8, 238-9.

63. "Tetramethylpyrazine, 2-15 mg/kg i.v., caused prominent systemic and coronary vasodilation"

Dai XZ, Bache RJ. Coronary and systemic hemodynamic effects of tetramethylpyrazine in the dog. *J Cardiovasc Pharmacol.* 1985 Sep-Oct;7(5):841-9.

64. "One of the valepotriatic fractions [from the valerian roots] ... is characterized .... by coronarodilating .... action."

Petkov, V. Plants and hypotensive, antiatheromatous and coronarodilatating action. *Am J Chin Med.* 1979 Autumn;7(3):197-236.

65. "Vasodilating effect of crude platycodin in anesthetized dogs"

Kato H, Suzuki S, Nakao K, Lee EB, Takagi K. Vasodilating effect of crude platycodin in anesthetized dogs. *Jpn J Pharmacol.* 1973 Oct;23(5):709-16.

66. "Acetazolamide nevertheless caused a rapid vasodilation in the brain and over a wide range of PCO<sub>2</sub>'s. We suggest that this agent has a local vasodilator effect on the cerebral arterioles".

Hauge A, Nicolaysen G, Thoresen M. Acute effects of acetazolamide on cerebral blood flow in man. *Acta Physiol Scand*. 1983 Feb;117(2):233-9.

67. "The diameters of the right and left ovarian and uterine veins were measured. The largest significant increases in diameter, particularly after 21 days, were observed in mice treated with testosterone, dihydrotestosterone, estrone, estradiol-17beta, and progesterone".

Forbes TR, Glassen G. Steroid compounds and the dilatation of ovarian and uterine veins in the mouse. *Am J Obstet Gynecol*. 1972 Jul 1;113(5):678-80.

68. "Malva rotundifolia, a potential vasodilator."

Kratzer KE, Greif JM. Malva rotundifolia, a potential vasodilator. *J Am Osteopath Assoc*. 1969 Jun;68(10):1029-35.

69. "The alkyl ether analogs of phosphatidylcholine (formerly designated as the antihypertensive polar renomedullary lipid or APRL) are orally active vasodilators. They cause a prolonged depressor effect due to a decrease in peripheral vascular resistance."

Muirhead EE, Byers LW, Desiderio DM, Brooks B, Brosius WM. Antihypertensive lipids from the kidney: alkyl ether analogs of phosphatidylcholine. *Fed Proc*. 1981 Jun;40(8):2285-90.

70. "Alpha-hANP (3 micrograms/kg per min) resulted in a rapid and marked fall of blood pressure and of total peripheral resistance but with no change in cardiac output in both strains. alpha-hANP decreased vascular resistance in most organs and there was a redistribution of renal blood flow. Thus, the acute hypotensive effect of alpha-hANP is probably related to a vasodilator action."

Fujioka S, Tamaki T, Fukui K, Okahara T, Abe Y. Effects of a synthetic human atrial natriuretic polypeptide on regional blood flow in rats. *Eur J Pharmacol*. 1985 Feb 26;109(2):301-4.

71. "sANF does exhibit a profound regional vasodilator selectivity which can be explained, in part, by changes in receptor density".

Winqvist RJ, Napier MA, Vandlen RL, Arcuri K, Keegan ME, Faison EP, Baskin EP. Pharmacology and receptor binding of atrial natriuretic factor in vascular smooth muscle. *Clin Exp Hypertens A*. 1985;7(5-6):869-86.

72. "These results suggest that brovincamine produces a vasodilation via a slow Ca<sup>2+</sup>-channel blockade". Calcium antagonistic action involved in

vasodilation by brovincamine. Katsuragi T, Ohba M, Mori R, Kushiku K, Furukawa T. *Gen Pharmacol*. 1984;15(1):43-5.

73. "The total alkaloid sum of *Vinca herbacea* .... Produces a continuous decrease of blood pressure ... Central, ganglioblocking and peripheral vascular mechanisms underlie this hypotensive action".

Petkov, V. Plants and hypotensive, antiatheromatous and coronarodilatating action. *Am J Chin Med*. 1979 Autumn;7(3):197-236.

74. "With respect to the cardiovascular action of the alkaloid protopin a marked vasodilating effect was observed on the blood vessels of isolated rabbit ear."

Petkov, V. Plants and hypotensive, antiatheromatous and coronarodilatating action. *Am J Chin Med*. 1979 Autumn;7(3):197-236.

75. "A positive property of *Astragalus* is the combination of its hypotensive effect with .... a coronarodilating action. .... Some of the other effects of different *Astragalus* subspecies such as vasodilating .... Might also be explained by the presence of gamma-aminobutyric acid."

Petkov, V. Plants and hypotensive, antiatheromatous and coronarodilatating action. *Am J Chin Med*. 1979 Autumn;7(3):197-236.

76. "A series of beta-hydroxylamine-phenylpropyl hydroxamic acids .... can be classified as direct acting vasodilators."

Kehl H, Fountain K, Early T. Structure-activity studies of hydroxamic acids as direct vasodilators. *Arzneimittelforschung*. 1978;28(11):2087-92.

77. "Molsidomine is a venous vasodilator with useful pharmacokinetic properties".

Witchitz S, Kolsky H, Moisson P, Valette H. Ergometric study of a new vasodilator agent in angina: molsidomine. Value of combination with beta-blockaders. *Arch Mal Coeur Vaiss*. 1981 Apr;74(4):463-71.

78. "The vasodilator activity of doxepin was probably a manifestation of the smooth muscle spasmolytic properties of the drug"

Constantine JW, Scriabine A, Smith SG, McShane WK, Booher KD. Antispasmodic And Vasolidator Activities Of Doxepin. *J New Drugs*. 1964 Sep-Oct;38:249-57.

79. "Type 4 agents (perhexiline, lidoflazine and bepridil) have a broader pharmacologic profile; they block calcium fluxes in the heart, in the peripheral vessels or in both".  
Singh BN, Baky S, Nademanee K. *Am J Cardiol.* 1985 Jan 25;55(3):214B-221B.
80. "The relaxant and antispasmodic effects of streptidin on smooth muscles".  
Altinkurt O. The relaxant and antispasmodic effects of streptidin on smooth muscles. *Turk Hij Tecr Biyol Derg.* 1970;30(3):242-4.
81. "The antithrombotic activity of viquidil, a cerebral vasodilator".  
Sim AK, Uzan A. The antithrombotic activity of viquidil, a cerebral vasodilator. *Arzneimittelforschung.* 1979;29(3):508-11.
82. "Relative experimental coronary vasodilator potencies of papaverine and its ethyl analogue, ethaverine (diquinol, perparin)."  
Winder CV, Thomas RW, Kamm O. Relative experimental coronary vasodilator potencies of papaverine and its ethyl analogue, ethaverine (diquinol, perparin). *J Pharmacol Exp Ther.* 1950 Dec;100(4:1):482-8.
83. "Like PETN, papaverine and ethaverine provoked an appropriate redistribution during a second period. These results are discussed in terms of the selectivity of coronary dilator action on large or small vessels".  
Lacroix P, Linee P, Le Polles JB. Effects of some coronary vasodilator drugs on collateral hemodynamics after chronic myocardial ischemia in the anesthetized dog: appropriate or inappropriate redistribution? *J Pharmacol Exp Ther.* 1978 Mar;204(3):645-54.
84. "Dilazep .... dilated the vessel".  
Suzuki K, Niho T, Shimora M, Ito C, Yamaguchi K, Ohnishi H, Asano M. Effect of antianginal agents on arteriolar diameter in normal and cholesterol-fed rabbits. *Int J Microcirc Clin Exp.* 1984;3(1):49-58.
85. "Vasodilating effect of ethyl apovincamate on conjunctival vessels".  
Brooser G, Anda L, Doman J. Vasodilating effect of ethyl apovincamate on conjunctival vessels and simultaneous observation of parameters indicating adverse effect. *Arzneimittelforschung.* 1976;26(10a):1975-7.

86. "GABA increases total cerebral blood flow .... vasodilation induced by GABA".

Alborch E, Torregrosa G, Terrasa JC, Estrada C. GABA receptors mediate cerebral vasodilation in the unanesthetized goat. *Brain Res.* 1984 Oct 29;321(1):103-10.

87. "Bupicomide .... is acting as a direct vasodilator".

Velasco M, Gilbert CA, Rutledge CO, McNay JL. Antihypertensive effect of a dopamine beta hydroxylase inhibitor, bupicomide: a comparison with hydralazine. *Clin Pharmacol Ther.* 1975 Aug;18(2):145-53.

88. "These results indicate that hypotension induced rapidly after intravenous administration of fusaric acid or 5-(4'-chlorobutyl) picolinic acid is not due to the enzyme inhibition, but rather to the direct depression of cardiac function and decrease in peripheral vascular resistance".

Furuta Y, Washizaki M. Effects of fusaric acid and its derivative on the cardiovascular system. *Nippon Yakurigaku Zasshi.* 1976 Mar;72(2):139-44.

89. "Part of the mechanism of hormone-induced mesenteric vasodilatation may involve a direct relaxing effect of the hormones on vascular smooth muscle".

Fara JW. Effects of gastrointestinal hormones on vascular smooth muscle. *Am J Dig Dis.* 1975 Apr;20(4):346-53.

90. "Secretin .... evoked dose-dependent vasodilatation of the hepatic arterial vascular bed".

Richardson PD, Withrington PG. The vasodilator actions of isoprenaline, histamine, prostaglandin E<sub>2</sub>, glucagon and secretin on the hepatic arterial vascular bed of the dog. *Br J Pharmacol.* 1976 Aug;57(4):581-8.

91. "Secretin produced similar vasodilation in all organs .... duodenum, jejunum, heart, kidney, forelimb, spleen, and the skin and muscle of the forelimb".

Chou CC, Hsieh CP, Dabney JM. Comparison of vascular effects of gastrointestinal hormones on various organs. *Am J Physiol.* 1977 Feb;232(2):H103-9.

92. "Cetiedil (Stratene) has strong papaverine-like and weak atropine-like properties. It brings about peripheral vasodilation".

Boissier JR, Aurousseau M, Giudicelli JF, Duval D. Pharmacological findings on cetiedil. *Arzneimittelforschung*. 1978;28(12):2222-8.

93. "Etafenone, a new coronary vasodilator with antiarrhythmic properties". Hashimoto K, Satoh H, Imai S. Effects of etafenone and antiarrhythmic drugs on Na and Ca channels of guinea pig atrial muscle. *J Cardiovasc Pharmacol*. 1979 Sep-Oct;1(5):561-70.

94. "Inhibitory effect of etafenone hydrochloride on platelet aggregation". Ujiie A, Komatsu H, Kubota T, Hamano S, Naito J. Studies on the inhibitory effect of etafenone hydrochloride on platelet aggregation. *Nippon Yakurigaku Zasshi*. 1983 Jun;81(6):493-8.

95. "N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide .... produces relaxation of isolated vascular strips". Hidaka H, Asano M, Iwadare S, Matsumoto I, Totsuka T, Aoki N. A novel vascular relaxing agent, N-(6--aminohexyl)-5-chloro-1-naphthalensulfonamide which affects vascular smooth muscle actomyosin. *J Pharmacol Exp Ther*. 1978 Oct;207(1):8-15.

96. "In vivo, .... 2-nicotinamidoethyl nitrate .... may have a more potent vasodilating action". Inoue T, Kanmura Y, Fujisawa K, Itoh T, Kuriyama H. Effects of 2-nicotinamidoethyl nitrate (nicorandil; SG-75) and its derivative on smooth muscle cells of the canine mesenteric artery. *J Pharmacol Exp Ther*. 1984 Jun;229(3):793-802.

97. "A non-competitive antagonism of noradrenaline-induced contractions by the *Phyllanthus sellowianus* alkaloid was also demonstrated on aortic rings". Calixto JB, Yunes RA, Neto AS, Valle RM, Rae GA. Antispasmodic effects of an alkaloid extracted from *Phyllanthus sellowianus*: a comparative study with papaverine. *Braz J Med Biol Res*. 1984;17(3-4):313-21.

98. "Vasorelaxant action of caroverine fumarate". Ishida Y, Ozaki H, Shibata S. Vasorelaxant action of caroverine fumarate (a quinoxaline derivative), a calcium-blocking agent. *Br J Pharmacol*. 1980;71(1):343-8.

99. "Malva rotundifolia, a potential vasodilator."

Kratzer KE, Greif JM. *Malva rotundifolia*, a potential vasodilator. *J Am Osteopath Assoc*. 1969 Jun;68(10):1029-35.

100. "The hypothermia in response to Shan-dou-gen was brought about by both cutaneous vasodilatation and decreased metabolic heat production."  
Lin MT, Chi ML, Han PW. Effects of Shan-dou-gen (*Euchresta formosana*) on metabolic, respiratory and vasomotor activities as well as body temperature in rats. *Am J Chin Med*. 1980 Spring-Summer;8(1-2):96-103.

101. "The latter alkaloid has an antihypertensive effect which is not found in oliveridine, only hypotensive by a relaxant close to papaverine action on vascular smooth muscles"

Quevauviller A, Hamonniere M. [Activity of the principal alkaloids of *Polyalthia oliveri* Engler (Annonaceae) on the central nervous system and the cardiovascular system]. *C R Acad Sci Hebd Seances Acad Sci D*. 1977 Jan 3;284(1):93-6.

102. "Sinomenine is a unique plant alkaloid, as it potently releases histamine in association with degranulation of tissue mast cells in mammalian tissues. This action occurs preferentially in the skin and joint capsules. The released histamine is responsible for the dominant pharmacological actions of sinomenine, such as vasodilatation, increased vascular permeability".

Yamasaki H. Pharmacology of sinomenine, an anti-rheumatic alkaloid from *Sinomenium acutum*. *Acta Med Okayama*. 1976 Feb;30(1):1-20.

103. "Beta-Endorphin .... dilated in vivo the arteriole of the microcirculatory system in hamster cheek pouch".

Wong TM, Koo A, Li CH. Beta-endorphin. Vasodilating effect on the microcirculatory system of hamster cheek pouch. *Int J Pept Protein Res*. 1981 Oct;18(4):420-2.

104. "Feeding 75 g of butter to healthy males (group I, n = 10 cases), enhanced the tendency of platelet adhesiveness (PAd) and platelet aggregation (PAg) to a significant level at the end of 4 h".

Bordia A, Verma SK. Effect of vitamin C on platelet adhesiveness and platelet aggregation in coronary artery disease patients. *Clin Cardiol*. 1985 Oct;8(10):552-4.



105. "Cis-unsaturated fatty acids .... inhibited platelet shape change, aggregation".  
MacIntyre DE, Hoover RL, Smith M, Steer M, Lynch C, Karnovsky MJ, Salzman EW. Inhibition of platelet function by cis-unsaturated fatty acids. *Blood*. 1984 Apr;63(4):848-57.
106. "All the cis-unsaturated fatty acids tested inhibited aggregation".  
Kitagawa S, Endo J, Kametani F. Effects of long-chain cis-unsaturated fatty acids and their alcohol analogs on aggregation of bovine platelets and their relation with membrane fluidity change. *Biochim Biophys Acta*. 1985 Sep 10;818(3):391-7.
107. "DHA .... inhibited aggregation of platelets".  
Rao GH, Radha E, White JG. Effect of docosahexaenoic acid (DHA) on arachidonic acid metabolism and platelet function. *Biochem Biophys Res Commun*. 1983 Dec 16;117(2):549-55.
108. "A semisynthetic diet containing adequate amounts of vitamin E and 10% (w/w) of a mixture of polyunsaturated oils subjected to heating and characterized by elevated indexes of thermal alteration (polar component, dimer triglyceride, altered triglyceride contents and reduced alpha-tocopherol levels) was fed to growing male rats for a period of eight weeks. It resulted in a selective alteration of the production of vascular eicosanoids (elevation of platelet thromboxane formation and decrease of vascular prostacyclin release)".  
Giani E, Masi I, Galli C. Heated fat, vitamin E and vascular eicosanoids. *Lipids*. 1985 Jul;20(7):439-48.
109. "Sulphated polysaccharide (S-Lim) .... isolated from mussel broth .... displayed an anticoagulant activity .... found to inhibit thrombin-induced platelet aggregation".  
Nilsson IM, Rothman U, Stenberg P, Frohm B, Persson NH. A novel semi-synthetic sulphated polysaccharide with potent antithrombin activity. *Br J Haematol*. 1982 Feb;50(2):335-43.
110. "Dihomogammalinolenic acid (20:3 omega 6) is more anti-aggregatory than eicosapentaenoic (20:5 omega 3) in a platelet-endothelial cell mixture."  
Lagarde M, Burtin M, Dechavanne M, Sicard B, Coiffier B. Dihomogammalinolenic acid (20:3 omega 6) is more anti-aggregatory than

eicosapentaenoic (20:5 omega 3) in a platelet-endothelial cell mixture. Prostaglandins Med. 1980 Mar;4(3):177-83.

111. "The rank order of four carrageenans tested as inducers of human platelet aggregation was the same (iota greater than lambda greater than gelcarin greater than kappa) as their relative inflammatory potencies in vivo. All four carrageenans caused some precipitation of plasma proteins, and induced aggregation in platelet-rich plasma or washed platelet suspensions." McMillan RM, MacIntyre DE, Gordon JL. Stimulation of human platelets by carrageenans. J Pharm Pharmacol. 1979 Mar;31(3):148-52.

112. "New platelet aggregation inhibitors from Tan-Shen; radix of Salvia miltiorrhiza Bunge." Onitsuka M, Fujiu M, Shinma N, Maruyama HB. New platelet aggregation inhibitors from Tan-Shen; radix of Salvia miltiorrhiza Bunge. Chem Pharm Bull (Tokyo). 1983 May;31(5):1670-5.

113. "N-acetylcysteine potentiated markedly the inhibitory effect of nitroglycerin on platelet aggregation" Loscalzo J. N-Acetylcysteine potentiates inhibition of platelet aggregation by nitroglycerin. J Clin Invest. 1985 Aug;76(2):703-8.

114. "It is concluded that NAC [N-acetylcysteine] potentiates the vasodilator effects of NTG [nitroglycerin] in man" Horowitz JD, Antman EM, Lorell BH, Barry WH, Smith TW. Potentiation of the cardiovascular effects of nitroglycerin by N-acetylcysteine. Circulation. 1983 Dec;68(6):1247-53.

115. "Flavin adenine dinucleotide .... could inhibit H<sub>2</sub>O<sub>2</sub>-induced platelet aggregation." Higashi O, Ishigaki W, Hashimoto T. Effects of riboflavin-2',3',4',5'-tetrabutryrate and flavin adenine dinucleotide on the platelet aggregation induced by hydrogen peroxide. Tohoku J Exp Med. 1978 Apr;124(4):323-9.

116. "Flavine adenine dinucleotide (FAD) may inhibit not only the aggregation but also ATP release of platelets in vitro". Shimada K, Takahashi W, Watanabe A, Matsuno K, Higashi O. Further studies on the effects of flavine adenine dinucleotide on the platelet functions. Tohoku J Exp Med. 1983 May;140(1):81-8.

117. "Auranofin (AF), at a concentration of 10 micrograms/ml, was found to be a potent inhibitor of ADP-, epinephrine-, or collagen-induced platelet aggregation".

Nathan I, Finkelstein AE, Walz DT, Dvilansky A. Studies of the effect of auranofin, a new antiarthritic agent, on platelet aggregation. *Inflammation*. 1982 Mar;6(1):79-85.

118. "Injectio Salvia Miltiorrhizae .... inhibited platelet aggregation and serotonin release induced by either ADP or epinephrine in a dose dependent manner."

Wang Z, Roberts JM, Grant PG, Colman RW, Schreiber AD. The effect of a medicinal Chinese herb on platelet function. *Thromb Haemost*. 1982 Dec 27;48(3):301-6.

119. "Quercetin and 12 other natural flavonoid aglycones inhibit washed human platelet aggregation and secretion of serotonin induced by ADP, collagen or thrombin."

Beretz A, Cazenave JP, Anton R. Inhibition of aggregation and secretion of human platelets by quercetin and other flavonoids: structure-activity relationships. *Agents Actions*. 1982 Jul;12(3):382-7.

120. "Mebeverine bound to beta 2- and alpha-receptors and inhibited phosphodiesterase activity".

Greenslade FC, Scott CK, Newquist KL, Krider KM, Chasin M. Heterogeneity of biochemical actions among vasodilators. *J Pharm Sci*. 1982 Jan;71(1):94-100

121. "Pharmacological and Toxicological Study of a Coronary Vasodilator: Ethyl Flavone-7-Oxyacetate.]".

Morin H, Roux M, Jachiet MT. Pharmacological and Toxicological Study of a Coronary Vasodilator: Ethyl Flavone-7-Oxyacetate. *Therapie*. 1964 Nov-Dec;19:1555-68.

122. "Fendiline dose dependently increased coronary flow by up to 200% .... The counteraction of the "washout effect" by fendiline .... is most likely due to the opening of additional (previously closed) capillaries".

Kukovetz WR, Poch G, Holzmann S, Paietta E. Pharmacological Properties of Fendiline in Cardiac and Smooth Muscle. *Arzneimittelforschung*. 1976;26(7):1321-30.

123. "Dantrolene blocks intracellular calcium release in smooth muscle: competitive antagonism of thromboxane A<sub>2</sub>".  
Ally AI, Horrobin DF, Manku MS, Morgan RO, Karmazyn M, Karmali RA, Cunnane SC. Dantrolene blocks intracellular calcium release in smooth muscle: competitive antagonism of thromboxane A<sub>2</sub>. *Can J Physiol Pharmacol*. 1978 Jun;56(3):520-3.
124. "Oxybutynin has a vasodilating action probably ascribable to its anticholinergic and antispasmodic actions".  
Misawa M, Hosokawa T, Kamei J, Yanaura S, Fujii Y, Watanabe K, Uehara M, Kasama T. Effects of oxybutynin on the cardiovascular system in dogs. *Nippon Yakurigaku Zasshi*. 1984 Oct;84(4):395-406.
125. "A vasodilator agent from the leaves of the ginvgoree".  
Fischer M. A vasodilator agent from the leaves of the ginvgoree. *Landarzt*. 1967 Apr 20;43(11):iv, vi ix
126. "Inhibition of human and rat platelet aggregation by extracts of Mo-er (Auricularia auricula)."  
Agarwal KC, Russo FX, Parks RE Jr. Inhibition of human and rat platelet aggregation by extracts of Mo-er (Auricularia auricula). *Thromb Haemost*. 1982 Oct 29;48(2):162-5.
127. "Coffee extracts contain compounds which are active in inhibiting platelet aggregation".  
Bydlowski SP, Yunker RL, Rymaszewski Z, Subbiah MT. Coffee extracts inhibit platelet aggregation in vivo and in vitro. *Int J Vitam Nutr Res*. 1987;57(2):217-23.
128. "Collagen-induced platelet aggregation and thromboxane release is inhibited, in a concentration response relationship, by preincubation of gel-filtered platelets with melatonin".  
Leach CM, Thorburn GD. A comparison of the inhibitory effects of melatonin and indomethacin on platelet aggregation and thromboxane release. *Prostaglandins*. 1980 Jul;20(1):51-6.
129. "If human platelets react to uric acid in the same manner as rat platelets this might explain the link that has been suggested between hyperuricaemia and ischaemic heart disease. In that event diets high in

nucleic acids might be contra-indicated in people at risk from ischaemic heart disease”.

Winocour PD, Turner MR, Taylor TG, Munday KA. Platelet aggregation in rats in relation to hyperuricaemia induced by dietary single-cell protein and to protein deficiency. *Thromb Haemost.* 1978 Apr 30;39(2):346-59.

130. “Clinical and experimental study on anti-platelet aggregation effect of d-catechin”.

He YS. Clinical and experimental study on anti-platelet aggregation effect of d-catechin. *Zhong Xi Yi Jie He Za Zhi.* 1982 Jan;2(1):15-8.

131. “The effect of selenium supplementation on in vivo platelet aggregability was studied by measuring plasma levels of beta-thromboglobulin and platelet factor 4, two proteins secreted concomitant with aggregation. beta-thromboglobulin diminished 7.5 +/- 11.0 ng/ml and platelet factor 7.6 +/- 11.0 ng/ml during selenium supplementation despite no change in platelet glutathione peroxidase activity.”

Stead NW, Leonard S, Carroll R. Effect of selenium supplementation on selenium balance in the dependent elderly. *Am J Med Sci.* 1985 Dec;290(6):228-33.

132. “The aggravation in selenium deficient mice may be due to enhanced platelet aggregation and suppressed formation of prostacyclin (PGI<sub>2</sub>) in the arterial all.”

Masukawa T, Goto J, Iwata H. Impaired metabolism of arachidonate in selenium deficient animals. *Experientia.* 1983 Apr 15;39(4):405-6.

133. “In animals maintained on a semisynthetic diet containing sucrose (62%) as the only carbohydrate source, platelet adhesiveness increased as compared with that in rats fed a normal chow pellet.”

Suzuki K. Effects of S-8527 (1, 1-bis (4'-(1"-carboxy-1"-methylpropoxy) phenyl) cyclohexane), a new hypolipidemic compound, on platelet aggregation, adhesiveness and blood coagulation in rats. *Jpn J Pharmacol.* 1975 Aug;25(4):393-9.

134. “The effect of ascorbic acid (A.A.) was compared to that of HCl and citric acid (C.A.). ADP- and collagen-induced aggregation of normal platelets were significantly impaired by both A.A. and C.A.”

Cowan DH, Graham RC Jr, Shook P, Griffin R. The influence of ascorbic acid on platelet structure and function. *Thromb Diath Haemorrh*. 1975 Sep 30;34(1):50-62.

135. "Citrate appears to inhibit aggregation as well as MDA synthesis"  
Huijgens PC, van den Berg CA, Voetdijk AM, Imandt LM. The influence of citrate on platelet aggregation and malondialdehyde production. *Scand J Haematol*. 1983 Aug;31(2):129-32.

136. "The first pharmacological characterization of vernolepin revealed ... an antiaggregating and disaggregating activity against rabbit platelet aggregation induced by arachidonic acid"  
Laekeman GM, Mertens J, Totte J, Bult H, Vlietinck AJ, Herman AG. Isolation and pharmacological characterization of vernolepin. *J Nat Prod*. 1983 Mar-Apr;46(2):161-9.

137. "Bromelain therapy leads to formation of platelets with increased resistance to aggregation".  
Felton GE. Fibrinolytic and antithrombotic action of bromelain may eliminate thrombosis in heart patients. *Med Hypotheses*. 1980 Nov;6(11):1123-33.

138. "The content of cholesterol in red cell and platelet membranes was lowered in rabbits with experimental atherosclerosis after intravenous injection of positively charged micelles of soybean phosphatidylcholine. That lowering was accompanied by a reduction in membrane microviscosity, rise of the activity of Na,K- and Ca-ATPases of red cells, and a decrease in the rate of the ADP- and collagen-induced platelet aggregation."  
Borodin EA, Lanio ME, Khalilov EM, Markin SS, Torkhovskaia TI. Extraction of cholesterol from biological membranes with positively charged micelles of phosphatidylcholine. *Biull Eksp Biol Med*. 1985 Feb;99(2):164-6.

139. "Addition of essential oil of garlic inhibited in-vitro platelet aggregation induced by ADP, epinephrine or collagen; the effect was dose-related. Oral administration of garlic also decreased platelet aggregation. Thus, garlic seems to inhibit some aspects of thrombus formation."  
Bordia A. Effect of garlic on human platelet aggregation in vitro. *Atherosclerosis*. 1978 Aug;30(4):355-60.

140. "It was concluded that the observed antiplatelet activity of onion relates to the presence of a non-polar, heat stable inhibitor of thromboxane synthesis. This appears to be the first demonstration of this type of inhibitor present in significant quantities in a common foodstuff."

Makheja AN, Vanderhoek JY, Bailey JM. Effects of onion (*Allium cepa*) extract on platelet aggregation and thromboxane synthesis. *Prostaglandins Med.* 1979 Jun;2(6):413-24.

141. "Aqueous extracts of onion, garlic and ginger inhibited platelet aggregation induced by several aggregation agents, including arachidonate (AA), in a dose-dependent manner."

Srivastava KC. Aqueous extracts of onion, garlic and ginger inhibit platelet aggregation and alter arachidonic acid metabolism. *Biomed Biochim Acta.* 1984;43(8-9):S335-46.

142. "The platelets ability to aggregate, whether spontaneously or by induction was found to be statistically significantly reduced [by an artichoke extract as a preparation called Cynarex]. The spontaneous aggregation after two years of Cynarex administration was reduced on average by 51%."

Woyke M, Cwajda H, Wojcicki J, Kosmider K. [Platelet aggregation in workers chronically exposed to carbon disulfide and subjected to prophylactic treatment with Cynarex]. *Med Pr.* 1981;32(4):261-4.

143. "Cholesterolemia and in vitro platelet aggregation by ADP dropped significantly in subjects fed the canbra oil diet."

Jacotot B, Winchenne N, Navarro N, N'Guyen A, Mendy F, Beaumont JL. Comparative effects of canbra oil and butter on lipdemia, vitamin A tolerance and thrombosis factors in man. *J Med.* 1978;9(6):471-81.

144. "Reduction in platelet aggregation by the oral administration of Moutan Cortex might be ascribed to a decrease in thromboxane synthesis and that paeonol might play an important role in the antiaggregatory effect of Moutan Cortex because of its potent inhibitory effect on platelet aggregation and thromboxane formation."

Hirai A, Terano T, Hamazaki T, Sajiki J, Saito H, Tahara K, Tamura Y, Kumagai A. Studies on the mechanism of antiaggregatory effect of Moutan Cortex. *Thromb Res.* 1983 Jul 1;31(1):29-40.

145. "Low dalton compounds from aqueous dialysates of several edible fungi have demonstrated inhibition of platelet aggregation in vitro. The

species of fungi included *Auricularia polytricha* (black tree fungus), *Cortinellus shiitake* (shiitake mushroom), *Agaricus biporus*, and *Auriculariaceae* sp. (white tree fungus)."

Hokama Y, Hokama JL. In vitro inhibition of platelet aggregation with low dalton compounds from aqueous dialysates of edible fungi. *Res Commun Chem Pathol Pharmacol*. 1981 Jan;31(1):177-80.

146. "The effect of hexobendine, pentoxifylline and of the combination Instenon, containing hexobendine, on the dynamic viscosity of blood-isotonic and hyperosmolal suspensions of human and rat erythrocytes was studied. Hexobendine caused a statistically significant reduction of viscosity beginning at 10(-4) M, under hyperosmolal conditions even at 10(-5) M." Winkler R, Moser M. [Effect of hexobendine and pentoxifylline on the viscosity of erythrocyte suspension]. *Wien Klin Wochenschr*. 1983 Mar 18;95(6):209-13.

147. "Binifibrate increased passage of a suspension of red blood cells at 80% haematocrit value through filters of 30-40 micron (Teitel's method), and erythrocyte deformability detectable by increase of flow rate through filters of pore size lesser than erythrocyte diameter (Schmid-Schonbein's method)." Bruseghini L, Freixes J, Andreoli R. Microhaemorheological properties of binifibrate. Part I: Experimental studies. *Arzneimittelforschung*. 1983;33(6):854-7.

148. "In patients with postthrombotic syndrome the medium blood stream velocity in the V. femoralis increased on the diseased side two hours after oral application of a high-dosed combination of ruscogenin ..."

Marshall M. [Varicose vein drugs--new attempts at objectivation of the effects of therapy]. *Fortschr Med*. 1984 Aug 16;102(29-30):772-4.

149. "The placenta contains such thrombotic factors as tissue thromboplastin, placental factor XIII, and placental urokinase inhibitor. On the other hand, there are some antithrombotic factors, for example, placental plasminogen activator and platelet aggregation inhibitor." Shidara Y. [Isolation and purification of placental coagulation inhibitor] *Nippon Sanka Fujinka Gakkai Zasshi*. 1984 Dec;36(12):2583-92.

150. "Platelet antiaggregating activity in the salivary secretion of the blood sucking bug *Rhodnius prolixus*."



Ribeiro JM, Garcia ES. Platelet antiaggregating activity in the salivary secretion of the blood sucking bug *Rhodnius prolixus*. *Experientia*. 1981 Apr 15;37(4):384-6.

151. "Saliva of mosquitoes .... inhibits the ADP- and collagen-mediated aggregation of platelets."

Ribeiro JM, Rossignol PA, Spielman A. Role of mosquito saliva in blood vessel location. *J Exp Biol*. 1984 Jan;108:1-7.

152. "Pilocarpine-induced saliva of the tick, *Ixodes dammini*, inhibited platelet aggregation triggered by ADP and collagen, as well as platelet-aggregation factor."

Ribeiro JM, Makoul GT, Levine J, Robinson DR, Spielman A. Antihemostatic, antiinflammatory, and immunosuppressive properties of the saliva of a tick, *Ixodes dammini*. *J Exp Med*. 1985 Feb 1;161(2):332-44.

153. "Sodium azide in low concentrations (0.1-10 micrometer) was found to have inhibitory effects on human platelet function. Primary aggregation induced by ADP, epinephrine, thrombin and the ionophore A 23187 was decreased."

Stibbe J, Holmsen H. Effects of sodium azide on platelet function. *Thromb Haemost*. 1977 Dec 15;38(4):1042-53.

154. "The hypothermia in response to Huang Chin application was brought about solely by cutaneous vasodilatation."

Lin MT, Liu GG, Wu WL, Chern YF. Effects of Chinese herb, Huang Chin (*Scutellaria baicalensis* George) on thermoregulation in rats. *Jpn J Pharmacol*. 1980 Feb;30(1):59-64.

155. "The sulphated polysaccharide (S-Lim) displayed an anticoagulant activity in a thrombin test system with human plasma."

Nilsson IM, Rothman U, Stenberg P, Frohm B, Persson NH. A novel semi-synthetic sulphated polysaccharide with potent antithrombin activity. *Br J Haematol*. 1982 Feb;50(2):335-43.

156. "An active fraction was isolated from an aqueous melon extract (*Cucurbitacea cucumis melo*) and was shown that it inhibits human platelet aggregation induced by epinephrine, ADP, collagen, thrombin, sodium arachidonate, prostaglandin endoperoxide analogue U-46619 and PAF-acether." [THE AUTHORS BELIEVED THE ACTIVE FRACTION WAS

ADENOSINE, WHICH WAS LINKED TO RAYNAUD'S BEFORE 1985. HOWEVER, I NOT FIND A CASE WHERE ADENOSINE WAS LINKED TO MELON BEFORE, OR WHERE A MELON EXTRACT HAD REDUCED PLATELET AGGREGATION]

Altman R, Rouvier J, Weisenberger H. Identification of platelet inhibitor present in the melon (*Cucurbitacea cucumis melo*). *Thromb Haemost*. 1985 Jun 24;53(3):312-3.

157. "Inhibition of arachidonate induced platelet aggregation was examined for three of the more potent inhibitors. 2-Benzoyloxyphenol and 2,4,6-trimethylphenol were more potent than indomethacin when assayed using a 2 min preincubation of inhibitor with platelets"

Dewhirst FE. Structure-activity relationships for inhibition of prostaglandin cyclooxygenase by phenolic compounds. *Prostaglandins*. 1980 Aug;20(2):209-22.

158. "In vivo treatment of morphine-addicted mice with AL ... [lipid mixture extracted from hen egg-yolk (Active-lipid, AL)] ... reversed the brain membrane hyperviscosity"

Heron DS, Shinitzky M, Samuel D. Alleviation of drug withdrawal symptoms by treatment with a potent mixture of natural lipids. *Eur J Pharmacol*. 1982 Sep 24;83(3-4):253-61.

159. "Fasting was discovered to lead to the reduction of blood plasma and red cell coagulation, to the deterioration of platelet aggregation, rise in the oxidized hemoglobin content, and to the increase in red cell resistance to peroxide hemolysis."

Muliar LA, Mishchenko VP, Loban' GA, Goncharenko LL, Bobyrev VN. [Effect of complete fasting on the coagulative and antioxidative properties of blood]. *Vopr Pitan*. 1984 Jul-Aug;(4):20-3.

160. "VLDL and LDL were more fluid from rabbits fed cocoa butter than from rabbits fed corn oil".

Berlin E, Young C Jr. Influence of dietary fats on the fluidity of the lipid domains of rabbit plasma lipoproteins. *Atherosclerosis*. 1980. Mar;35(3):229-41.

161. .... supplemented their normal diets with 0.45 g/kg/day guar gum for 4 weeks. They experienced a decrease in (1) plasma fibrinogen, (2) insulin requirement, (3) serum osmolality and (4) plasma viscosity; and an increase

in serum albumin and total serum protein concentrations. The decrease in plasma viscosity, which was statistically significant ....

Koepp P, Hegewisch S. Effects of guar on plasma viscosity and related parameters in diabetic children. *Eur J Pediatr*. 1981 Sep;137(1):31-3.

162. "Under appropriate conditions of flow, however, the addition of linear polymers of high mol. wt--of the order of  $10(5)$  to  $10(7)$  daltons--may cause the flow to increase as much as 3-fold and occasionally more without altering the driving pressure..... A marked fall in the pressure gradients of constant blood flows through pipes has also been observed upon the addition of polyacrylamide, poly(ethylene oxide), deoxyribonucleic acid, or a polysaccharide extracted from okra."

Polimeni PI, Ottenbreit B, Coleman P. Enhancement of aortic blood flow with a linear anionic macropolymer of extraordinary molecular length. *J Mol Cell Cardiol*. 1985 Jul;17(7):721-4.

163. "Optimal rheologic behavior was exhibited by normal RBC when their water content was in the normal range. A rise or a fall in cell hydration resulted in a decrease in cell deformability".

Gulley ML, Ross DW, Feo C, Orringer EP. The effect of cell hydration on the deformability of normal and sickle erythrocytes. *Am J Hematol*. 1982 Dec;13(4):283-91.

164. "Maximal arm blood flow was reduced by nearly 50% in hypohydration"

Nadel ER, Fortney SM, Wenger CB. Effect of hydration state of circulatory and thermal regulations. *J Appl Physiol*. 1980 Oct;49(4):715-21.

165. "Extracts of feverfew (*Tanacetum parthenium*) inhibited secretory activity in blood platelets and polymorphonuclear leucocytes (PMNs). Platelet aggregation was consistently inhibited but thromboxane synthesis was not"

Heptinstall S, White A, Williamson L, Mitchell JR. Extracts of feverfew inhibit granule secretion in blood platelets and polymorphonuclear leucocytes. *Lancet*. 1985 May 11;1(8437):1071-4.

166. "Tricholysine (triasin) and longolytin, isolated from cultural fluid of two similar lower fungi *Trichothecium roseum* and *Arthrobotrys longa*, exhibited anticoagulant and fibrinolytic properties after addition to blood plasma of experimental animals."

Serebriakova TN, Andreenko GV, Maksimova RA, Tsymanovich ST, Murashova NL. [Anticoagulating properties of fungal proteases tricholysine (triasse) and longolytin]. Vopr Med Khim. 1984 Sep-Oct;30(5):37-40. Russian.

## APPENDIX 2 – INDIRECT QUERY – PARKINSON’S DISEASE

([MECHANISMS] NOT ([PARKINSON'S CORE] OR [DIRECT RELATED])) AND [SEMANTIC CLASSES]

Where the direct related query has the same structure (([MECHANISMS] NOT [PARKINSON'S CORE]) AND [SEMANTIC CLASSES])

(MI NOT (C OR ((MD NOT C) AND S))) AND S

D= ((MD NOT C) AND S)

MI =

(“AGONIST RECEPTOR\*” OR “ANTAGONIST RECEPTOR\*” OR “ANTIOXIDANT ENZYMES” OR “ARYL HYDROCARBON RECEPTOR” OR (BAICALEIN OR BCL OR FLAVOPIRIDOL) OR CASPASES OR (“DOPAMINE NEURON\*” OR “DOPAMINERGIC NEURON\*”) OR “DOPAMINE RECEPTOR\*” OR “ENZYME INHIBITOR\*” OR ((ERK OR MEK) AND “MAP KINASE” AND INHIBIT\*) OR “ESTROGEN RECEPTOR\*” OR “GLUTATHIONE PEROXIDASE” OR “HEAT SHOCK PROTEIN\*” OR “MITOCHONDRIAL DYSFUNCTION” OR “MITOCHONDRIAL MEMBRANE\*” OR “MITOCHONDRIAL STRESS” OR “MOTOR ACTIVITY” OR “MPP INDUCED” OR MPTP OR “NERVE DEGENERATION” OR “OXIDATIVE DAMAGE” OR “PROTEASOME PATHWAY” OR “PROTEIN CARBONYL\*” OR “PROTEIN CATABOLISM” OR “PROTEIN DEGRADATION” OR “PROTEIN OXIDATION” OR “PROTEIN SYNTHESIS” OR “PROTEOLYTIC PATHWAY\*” OR “RECEPTOR BINDING” OR RECEPTORS, NMDA OR “SUPEROXIDE DISMUTASE” OR “THIOBARBITURIC ACID REACTIVE” OR UBIQUITIN) OR ((“AMYLOID BETA PROTEIN” AND ANTIOXIDANTS AND (APOPTOSIS OR “CELL DEATH” OR “CELL SURVIVAL” OR “ENZYME ACTIVATION” OR “FREE RADICALS” OR “LIPID PEROXIDATION” OR “NEUROPROTECTIVE AGENTS” OR “OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“AMYLOID BETA PROTEIN” AND APOPTOSIS AND (“CELL DEATH” OR “CELL SURVIVAL” OR “ENZYME ACTIVATION” OR “FREE RADICALS” OR “LIPID PEROXIDATION” OR “NEUROPROTECTIVE AGENTS” OR “OXIDATION-REDUCTION” OR

“OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
 “REACTIVE OXYGEN SPECIES”)) OR (“AMYLOID BETA PROTEIN”  
 AND “CELL DEATH” AND (“CELL SURVIVAL” OR “ENZYME  
 ACTIVATION” OR “FREE RADICALS” OR “LIPID PEROXIDATION”  
 OR “NEUROPROTECTIVE AGENTS” OR “OXIDATION-REDUCTION”  
 OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
 “REACTIVE OXYGEN SPECIES”)) OR (“AMYLOID BETA PROTEIN”  
 AND “CELL SURVIVAL” AND (“ENZYME ACTIVATION” OR “FREE  
 RADICALS” OR “LIPID PEROXIDATION” OR “NEUROPROTECTIVE  
 AGENTS” OR “OXIDATION-REDUCTION” OR “OXIDATION-  
 REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN  
 SPECIES”)) OR (“AMYLOID BETA PROTEIN” AND “ENZYME  
 ACTIVATION” AND (“FREE RADICALS” OR “LIPID  
 PEROXIDATION” OR “NEUROPROTECTIVE AGENTS” OR  
 “OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR  
 “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
 (“AMYLOID BETA PROTEIN” AND “FREE RADICALS” AND (“LIPID  
 PEROXIDATION” OR “NEUROPROTECTIVE AGENTS” OR  
 “OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR  
 “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
 (“AMYLOID BETA PROTEIN” AND “LIPID PEROXIDATION” AND  
 (“NEUROPROTECTIVE AGENTS” OR “OXIDATION-REDUCTION”  
 OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
 “REACTIVE OXYGEN SPECIES”)) OR (“AMYLOID BETA PROTEIN”  
 AND “NEUROPROTECTIVE AGENTS” AND (“OXIDATION-  
 REDUCTION” OR “OXIDATION-REDUCTION” OR “OXIDATIVE  
 STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“AMYLOID  
 BETA PROTEIN” AND “OXIDATION-REDUCTION” AND  
 (“OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
 “REACTIVE OXYGEN SPECIES”)) OR (“AMYLOID BETA PROTEIN”  
 AND “OXIDATION-REDUCTION” AND (“OXIDATIVE STRESS” OR  
 “REACTIVE OXYGEN SPECIES”)) OR (“AMYLOID BETA PROTEIN”  
 AND “OXIDATIVE STRESS” AND (“REACTIVE OXYGEN SPECIES”))  
 OR (ANTIOXIDANTS AND APOPTOSIS AND (“CELL DEATH” OR  
 “CELL SURVIVAL” OR “ENZYME ACTIVATION” OR “FREE  
 RADICALS” OR “LIPID PEROXIDATION” OR “NEUROPROTECTIVE  
 AGENTS” OR “OXIDATION-REDUCTION” OR “OXIDATION-  
 REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN  
 SPECIES”)) OR (ANTIOXIDANTS AND “CELL DEATH” AND (“CELL  
 SURVIVAL” OR “ENZYME ACTIVATION” OR “FREE RADICALS”

OR “LIPID PEROXIDATION” OR “NEUROPROTECTIVE AGENTS”  
OR “OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR  
“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
(ANTIOXIDANTS AND “CELL SURVIVAL” AND (“ENZYME  
ACTIVATION” OR “FREE RADICALS” OR “LIPID PEROXIDATION”  
OR “NEUROPROTECTIVE AGENTS” OR “OXIDATION-REDUCTION”  
OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
“REACTIVE OXYGEN SPECIES”)) OR (ANTIOXIDANTS AND  
“ENZYME ACTIVATION” AND (“FREE RADICALS” OR “LIPID  
PEROXIDATION” OR “NEUROPROTECTIVE AGENTS” OR  
“OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR  
“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
(ANTIOXIDANTS AND “FREE RADICALS” AND (“LIPID  
PEROXIDATION” OR “NEUROPROTECTIVE AGENTS” OR  
“OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR  
“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
(ANTIOXIDANTS AND “LIPID PEROXIDATION” AND  
(“NEUROPROTECTIVE AGENTS” OR “OXIDATION-REDUCTION”  
OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
“REACTIVE OXYGEN SPECIES”)) OR (ANTIOXIDANTS AND  
“NEUROPROTECTIVE AGENTS” AND (“OXIDATION-REDUCTION”  
OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
“REACTIVE OXYGEN SPECIES”)) OR (ANTIOXIDANTS AND  
“OXIDATION-REDUCTION” AND (“OXIDATION-REDUCTION” OR  
“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
(ANTIOXIDANTS AND “OXIDATION-REDUCTION” AND  
(“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
(ANTIOXIDANTS AND “OXIDATIVE STRESS” AND (“REACTIVE  
OXYGEN SPECIES”)) OR (APOPTOSIS AND “CELL DEATH” AND  
(“CELL SURVIVAL” OR “ENZYME ACTIVATION” OR “FREE  
RADICALS” OR “LIPID PEROXIDATION” OR “NEUROPROTECTIVE  
AGENTS” OR “OXIDATION-REDUCTION” OR “OXIDATION-  
REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN  
SPECIES”)) OR (APOPTOSIS AND “CELL SURVIVAL” AND  
(“ENZYME ACTIVATION” OR “FREE RADICALS” OR “LIPID  
PEROXIDATION” OR “NEUROPROTECTIVE AGENTS” OR  
“OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR  
“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
(APOPTOSIS AND “ENZYME ACTIVATION” AND (“FREE  
RADICALS” OR “LIPID PEROXIDATION” OR “NEUROPROTECTIVE

AGENTS" OR "OXIDATION-REDUCTION" OR "OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR (APOPTOSIS AND "FREE RADICALS" AND ("LIPID PEROXIDATION" OR "NEUROPROTECTIVE AGENTS" OR "OXIDATION-REDUCTION" OR "OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR (APOPTOSIS AND "LIPID PEROXIDATION" AND ("NEUROPROTECTIVE AGENTS" OR "OXIDATION-REDUCTION" OR "OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR (APOPTOSIS AND "NEUROPROTECTIVE AGENTS" AND ("OXIDATION-REDUCTION" OR "OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR (APOPTOSIS AND "OXIDATION-REDUCTION" AND ("OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR (APOPTOSIS AND "OXIDATIVE STRESS" AND ("REACTIVE OXYGEN SPECIES")) OR ("CELL DEATH" AND "CELL SURVIVAL" AND ("ENZYME ACTIVATION" OR "FREE RADICALS" OR "LIPID PEROXIDATION" OR "NEUROPROTECTIVE AGENTS" OR "OXIDATION-REDUCTION" OR "OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR ("CELL DEATH" AND "ENZYME ACTIVATION" AND ("FREE RADICALS" OR "LIPID PEROXIDATION" OR "NEUROPROTECTIVE AGENTS" OR "OXIDATION-REDUCTION" OR "OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR ("CELL DEATH" AND "FREE RADICALS" AND ("LIPID PEROXIDATION" OR "NEUROPROTECTIVE AGENTS" OR "OXIDATION-REDUCTION" OR "OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR ("CELL DEATH" AND "LIPID PEROXIDATION" AND ("NEUROPROTECTIVE AGENTS" OR "OXIDATION-REDUCTION" OR "OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR ("CELL DEATH" AND "NEUROPROTECTIVE AGENTS" AND ("OXIDATION-REDUCTION" OR "OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR ("CELL DEATH" AND "OXIDATION-REDUCTION" AND ("OXIDATION-REDUCTION" OR "OXIDATIVE STRESS" OR "REACTIVE OXYGEN SPECIES")) OR



(“CELL DEATH” AND “OXIDATION-REDUCTION” AND  
 (“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
 (“CELL DEATH” AND “OXIDATIVE STRESS” AND (“REACTIVE  
 OXYGEN SPECIES”)) OR (“CELL SURVIVAL” AND “ENZYME  
 ACTIVATION” AND (“FREE RADICALS” OR “LIPID  
 PEROXIDATION” OR “NEUROPROTECTIVE AGENTS” OR  
 “OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR  
 “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
 (“CELL SURVIVAL” AND “FREE RADICALS” AND (“LIPID  
 PEROXIDATION” OR “NEUROPROTECTIVE AGENTS” OR  
 “OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR  
 “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
 (“CELL SURVIVAL” AND “LIPID PEROXIDATION” AND  
 (“NEUROPROTECTIVE AGENTS” OR “OXIDATION-REDUCTION”  
 OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
 “REACTIVE OXYGEN SPECIES”)) OR (“CELL SURVIVAL” AND  
 “NEUROPROTECTIVE AGENTS” AND (“OXIDATION-REDUCTION”  
 OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
 “REACTIVE OXYGEN SPECIES”)) OR (“CELL SURVIVAL” AND  
 “OXIDATION-REDUCTION” AND (“OXIDATION-REDUCTION” OR  
 “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
 (“CELL SURVIVAL” AND “OXIDATION-REDUCTION” AND  
 (“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
 (“CELL SURVIVAL” AND “OXIDATIVE STRESS” AND (“REACTIVE  
 OXYGEN SPECIES”)) OR (“ENZYME ACTIVATION” AND “FREE  
 RADICALS” AND (“LIPID PEROXIDATION” OR  
 “NEUROPROTECTIVE AGENTS” OR “OXIDATION-REDUCTION” OR  
 “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
 “REACTIVE OXYGEN SPECIES”)) OR (“ENZYME ACTIVATION”  
 AND “LIPID PEROXIDATION” AND (“NEUROPROTECTIVE  
 AGENTS” OR “OXIDATION-REDUCTION” OR “OXIDATION-  
 REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN  
 SPECIES”)) OR (“ENZYME ACTIVATION” AND  
 “NEUROPROTECTIVE AGENTS” AND (“OXIDATION-REDUCTION”  
 OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR  
 “REACTIVE OXYGEN SPECIES”)) OR (“ENZYME ACTIVATION”  
 AND “OXIDATION-REDUCTION” AND (“OXIDATION-REDUCTION”  
 OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR  
 (“ENZYME ACTIVATION” AND “OXIDATION-REDUCTION” AND  
 (“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR

(“ENZYME ACTIVATION” AND “OXIDATIVE STRESS” AND (“REACTIVE OXYGEN SPECIES”)) OR (“FREE RADICALS” AND “LIPID PEROXIDATION” AND (“NEUROPROTECTIVE AGENTS” OR “OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“FREE RADICALS” AND “NEUROPROTECTIVE AGENTS” AND (“OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“FREE RADICALS” AND “OXIDATION-REDUCTION” AND (“OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“FREE RADICALS” AND “OXIDATION-REDUCTION” AND (“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“FREE RADICALS” AND “OXIDATIVE STRESS” AND (“REACTIVE OXYGEN SPECIES”)) OR (“LIPID PEROXIDATION” AND “NEUROPROTECTIVE AGENTS” AND (“OXIDATION-REDUCTION” OR “OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“LIPID PEROXIDATION” AND “OXIDATION-REDUCTION” AND (“OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“LIPID PEROXIDATION” AND “OXIDATION-REDUCTION” AND (“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“LIPID PEROXIDATION” AND “OXIDATIVE STRESS” AND (“REACTIVE OXYGEN SPECIES”)) OR (“NEUROPROTECTIVE AGENTS” AND “OXIDATION-REDUCTION” AND (“OXIDATION-REDUCTION” OR “OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“NEUROPROTECTIVE AGENTS” AND “OXIDATION-REDUCTION” AND (“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“NEUROPROTECTIVE AGENTS” AND “OXIDATIVE STRESS” AND (“REACTIVE OXYGEN SPECIES”)) OR (“OXIDATION-REDUCTION” AND “OXIDATION-REDUCTION” AND (“OXIDATIVE STRESS” OR “REACTIVE OXYGEN SPECIES”)) OR (“OXIDATION-REDUCTION” AND “OXIDATIVE STRESS” AND (“REACTIVE OXYGEN SPECIES”)) OR (“OXIDATION-REDUCTION” AND “OXIDATIVE STRESS” AND (“REACTIVE OXYGEN SPECIES”)))

MD =

(“PROTEIN AGGREGATION” AND “PROTEIN AGGREGATES”) OR (“PROTEIN AGGREGATION” AND “PROTEIN DEGRADATION”) OR (“PROTEIN AGGREGATION” AND “PROTEIN OXIDATION”) OR

("PROTEIN AGGREGATION" AND "LEWY BODIES") OR ("PROTEIN AGGREGATION" AND "ALPHA SYNUCLEIN") OR ("PROTEIN AGGREGATION" AND "OXIDATIVE STRESS") OR ("PROTEIN AGGREGATION" AND ("MONAMINE OXIDASE" AND INHIBIT\*)) OR ("PROTEIN AGGREGATION" AND PARKIN) OR ("PROTEIN AGGREGATION" AND UBIQUITIN) OR ("PROTEIN AGGREGATION" AND "TAU PROTEIN") OR ("PROTEIN AGGREGATION" AND "AMYLOID PRECURSOR PROTEIN") OR ("PROTEIN AGGREGATES" AND "PROTEIN DEGRADATION") OR ("PROTEIN AGGREGATES" AND "PROTEIN OXIDATION") OR ("PROTEIN AGGREGATES" AND "LEWY BODIES") OR ("PROTEIN AGGREGATES" AND "ALPHA SYNUCLEIN") OR ("PROTEIN AGGREGATES" AND "OXIDATIVE STRESS") OR ("PROTEIN AGGREGATES" AND ("MONAMINE OXIDASE" AND INHIBIT\*)) OR ("PROTEIN AGGREGATES" AND PARKIN) OR ("PROTEIN AGGREGATES" AND UBIQUITIN) OR ("PROTEIN AGGREGATES" AND "TAU PROTEIN") OR ("PROTEIN AGGREGATES" AND "AMYLOID PRECURSOR PROTEIN") OR ("PROTEIN DEGRADATION" AND "PROTEIN OXIDATION") OR ("PROTEIN DEGRADATION" AND "LEWY BODIES") OR ("PROTEIN DEGRADATION" AND "ALPHA SYNUCLEIN") OR ("PROTEIN DEGRADATION" AND "OXIDATIVE STRESS") OR ("PROTEIN DEGRADATION" AND ("MONAMINE OXIDASE" AND INHIBIT\*)) OR ("PROTEIN DEGRADATION" AND PARKIN) OR ("PROTEIN DEGRADATION" AND UBIQUITIN) OR ("PROTEIN DEGRADATION" AND "TAU PROTEIN") OR ("PROTEIN DEGRADATION" AND "AMYLOID PRECURSOR PROTEIN") OR ("PROTEIN OXIDATION" AND "LEWY BODIES") OR ("PROTEIN OXIDATION" AND "ALPHA SYNUCLEIN") OR ("PROTEIN OXIDATION" AND "OXIDATIVE STRESS") OR ("PROTEIN OXIDATION" AND ("MONAMINE OXIDASE" AND INHIBIT\*)) OR ("PROTEIN OXIDATION" AND PARKIN) OR ("PROTEIN OXIDATION" AND UBIQUITIN) OR ("PROTEIN OXIDATION" AND "TAU PROTEIN") OR ("PROTEIN OXIDATION" AND "AMYLOID PRECURSOR PROTEIN") OR ("LEWY BODIES" AND "ALPHA SYNUCLEIN") OR ("LEWY BODIES" AND "OXIDATIVE STRESS") OR ("LEWY BODIES" AND ("MONAMINE OXIDASE" AND INHIBIT\*)) OR ("LEWY BODIES" AND PARKIN) OR ("LEWY BODIES" AND UBIQUITIN) OR ("LEWY BODIES" AND "TAU PROTEIN") OR ("LEWY BODIES" AND "AMYLOID PRECURSOR PROTEIN") OR ("ALPHA SYNUCLEIN" AND "OXIDATIVE STRESS") OR ("ALPHA SYNUCLEIN" AND

(“MONAMINE OXIDASE” AND INHIBIT\*)) OR (“ALPHA  
 SYNUCLEIN” AND PARKIN) OR (“ALPHA SYNUCLEIN” AND  
 UBIQUITIN) OR (“ALPHA SYNUCLEIN” AND “TAU PROTEIN”) OR  
 (“ALPHA SYNUCLEIN” AND “AMYLOID PRECURSOR PROTEIN”) OR  
 (“OXIDATIVE STRESS” AND (“MONAMINE OXIDASE” AND  
 INHIBIT\*)) OR (“OXIDATIVE STRESS” AND PARKIN) OR  
 (“OXIDATIVE STRESS” AND UBIQUITIN) OR (“OXIDATIVE  
 STRESS” AND “TAU PROTEIN”) OR (“OXIDATIVE STRESS” AND  
 “AMYLOID PRECURSOR PROTEIN”) OR ((“MONAMINE OXIDASE”  
 AND INHIBIT\*) AND PARKIN) OR ((“MONAMINE OXIDASE” AND  
 INHIBIT\*) AND UBIQUITIN) OR ((“MONAMINE OXIDASE” AND  
 INHIBIT\*) AND “TAU PROTEIN”) OR ((“MONAMINE OXIDASE”  
 AND INHIBIT\*) AND “AMYLOID PRECURSOR PROTEIN”) OR  
 (PARKIN AND UBIQUITIN) OR (PARKIN AND “TAU PROTEIN”) OR  
 (PARKIN AND “AMYLOID PRECURSOR PROTEIN”) OR (UBIQUITIN  
 AND “TAU PROTEIN”) OR (UBIQUITIN AND “AMYLOID  
 PRECURSOR PROTEIN”) OR (“TAU PROTEIN” AND “AMYLOID  
 PRECURSOR PROTEIN”) OR ((RECEPTOR\* AND (DOPAMINE OR  
 ANTAGONIST OR NMDA OR AGONIST)) AND MPTP) OR  
 ((RECEPTOR\* AND (DOPAMINE OR ANTAGONIST OR NMDA OR  
 AGONIST)) AND (CELL\* AND APOPTOSIS)) OR ((RECEPTOR\* AND  
 (DOPAMINE OR ANTAGONIST OR NMDA OR AGONIST)) AND  
 (MITOCHONDRIA\* AND (IMPAIR\* OR DYSFUNCTION OR  
 SUPPRESSION OR BLOCKAGE\*))) OR ((RECEPTOR\* AND  
 (DOPAMINE OR ANTAGONIST OR NMDA OR AGONIST)) AND  
 (DOPAMIN\* AND NEUTRON\*)) OR ((RECEPTOR\* AND (DOPAMINE  
 OR ANTAGONIST OR NMDA OR AGONIST)) AND “DOPAMINE  
 INHIBIT\*”) OR (MPTP AND (CELL\* AND APOPTOSIS)) OR (MPTP  
 AND (MITOCHONDRIA\* AND (IMPAIR\* OR DYSFUNCTION OR  
 SUPPRESSION OR BLOCKAGE\*))) OR (MPTP AND (DOPAMIN\* AND  
 NEUTRON\*)) OR (MPTP AND “DOPAMINE INHIBIT\*”) OR ((CELL\*  
 AND APOPTOSIS) AND (MITOCHONDRIA\* AND (IMPAIR\* OR  
 DYSFUNCTION OR SUPPRESSION OR BLOCKAGE\*))) OR ((CELL\*  
 AND APOPTOSIS) AND (DOPAMIN\* AND NEUTRON\*)) OR ((CELL\*  
 AND APOPTOSIS) AND “DOPAMINE INHIBIT\*”) OR  
 ((MITOCHONDRIA\* AND (IMPAIR\* OR DYSFUNCTION OR  
 SUPPRESSION OR BLOCKAGE\*)) AND (DOPAMIN\* AND  
 NEUTRON\*)) OR ((MITOCHONDRIA\* AND (IMPAIR\* OR  
 DYSFUNCTION OR SUPPRESSION OR BLOCKAGE\*)) AND

“DOPAMINE INHIBIT\*”) OR ((DOPAMIN\* AND NEUTRON\*) AND  
“DOPAMINE INHIBIT\*”))

C =

PARKINSON\* NOT (PARKINSON\*[AU] OR WOLFF-PARKINSON\*)

S =

PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT  
EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR  
PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR  
ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR  
FLAVONOIDS OR "DIETARY SUPPLEMENTS"

## APPENDIX 3 – INDIRECT QUERY – MULTIPLE SCLEROSIS

### Thrust 1

(((((Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR Death)) AND ("Schwann Cell Cytoplasm" OR "Schwann Cell Proliferation" OR "Schwann Cell Differentiation")) AND (("Microglial Cell\*" OR "microglial Activation" OR "microglial Death")) OR ("Mitochondrial Dysfunction" OR "mitochondrial Swelling")) OR "Mitogen-Activated Protein Kinase Kinases" OR "Mitogen-Activated Protein Kinases" OR "Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*)) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR Death)) AND ("Microglial Cell\*" OR "microglial Activation" OR "microglial Death")) AND ((("Mitochondrial Dysfunction" OR "mitochondrial Swelling")) OR "Mitogen-Activated Protein Kinase Kinases" OR "Mitogen-Activated Protein Kinases" OR "Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*)) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR Death)) AND ("Mitochondrial Dysfunction" OR "mitochondrial Swelling")) AND ("Mitogen-Activated Protein Kinase Kinases" OR "Mitogen-Activated Protein Kinases" OR "Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*)) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR Death)) AND "Mitogen-Activated Protein Kinases" AND ("Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*)) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR Death)) AND "Mitogen-Activated Protein Kinase Kinases" AND ("Mitogen-Activated Protein Kinases" OR "Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*)) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR Death)) AND "Mitogen-Activated Protein Kinases" AND ("Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*)) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR Death)) AND "Glial Fibrillary Acidic Protein" AND ((Astrocyte\* AND

Reactiv\*) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*)  
 OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme  
 Inhibitors")) OR ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR  
 Differentiation OR Death)) AND (Astrocyte\* AND Reactiv\*) AND  
 ("Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve  
 Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR  
 ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR  
 Death)) AND "Oxidative Phosphorylation" AND ((Caspase-3 AND  
 Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme  
 Inhibitors")) OR ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR  
 Differentiation OR Death)) AND (Caspase-3 AND Activat\*) AND ("Nerve  
 Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR  
 ((Oligodendro\* AND (Progenitor\* OR Precursor\* OR Differentiation OR  
 Death)) AND "Nerve Degeneration" AND ("Enzyme Activation" OR  
 "Enzyme Inhibitors")) OR ((Oligodendro\* AND (Progenitor\* OR  
 Precursor\* OR Differentiation OR Death)) AND "Enzyme Activation" AND  
 ("Enzyme Inhibitors")) OR (("Schwann Cell Cytoplasm" OR "Schwann Cell  
 Proliferation" OR "Schwann Cell Differentiation") AND ("Microglial Cell\*"  
 OR "microglial Activation" OR "microglial Death") AND (("Mitochondrial  
 Dysfunction" OR "mitochondrial Swelling") OR "Mitogen-Activated Protein  
 Kinase Kinases" OR "Mitogen-Activated Protein Kinases" OR "Glial  
 Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*) OR "Oxidative  
 Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration"  
 OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR (("Schwann Cell  
 Cytoplasm" OR "Schwann Cell Proliferation" OR "Schwann Cell  
 Differentiation") AND ("Mitochondrial Dysfunction" OR "mitochondrial  
 Swelling") AND ("Mitogen-Activated Protein Kinase Kinases" OR  
 "Mitogen-Activated Protein Kinases" OR "Glial Fibrillary Acidic Protein"  
 OR (Astrocyte\* AND Reactiv\*) OR "Oxidative Phosphorylation" OR  
 (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme  
 Activation" OR "Enzyme Inhibitors")) OR (("Schwann Cell Cytoplasm" OR  
 "Schwann Cell Proliferation" OR "Schwann Cell Differentiation") AND  
 "Mitogen-Activated Protein Kinase Kinases" AND ("Mitogen-Activated  
 Protein Kinases" OR "Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND  
 Reactiv\*) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*)  
 OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme  
 Inhibitors")) OR (("Schwann Cell Cytoplasm" OR "Schwann Cell  
 Proliferation" OR "Schwann Cell Differentiation") AND "Mitogen-  
 Activated Protein Kinases" AND ("Glial Fibrillary Acidic Protein" OR  
 (Astrocyte\* AND Reactiv\*) OR "Oxidative Phosphorylation" OR (Caspase-

3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR  
 "Enzyme Inhibitors")) OR (("Schwann Cell Cytoplasm" OR "Schwann Cell  
 Proliferation" OR "Schwann Cell Differentiation") AND "Glial Fibrillary  
 Acidic Protein" AND ((Astrocyte\* AND Reactiv\*) OR "Oxidative  
 Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration"  
 OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR (("Schwann Cell  
 Cytoplasm" OR "Schwann Cell Proliferation" OR "Schwann Cell  
 Differentiation") AND (Astrocyte\* AND Reactiv\*) AND ("Oxidative  
 Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration"  
 OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR (("Schwann Cell  
 Cytoplasm" OR "Schwann Cell Proliferation" OR "Schwann Cell  
 Differentiation") AND "Oxidative Phosphorylation" AND ((Caspase-3 AND  
 Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme  
 Inhibitors")) OR (("Schwann Cell Cytoplasm" OR "Schwann Cell  
 Proliferation" OR "Schwann Cell Differentiation") AND (Caspase-3 AND  
 Activat\*) AND ("Nerve Degeneration" OR "Enzyme Activation" OR  
 "Enzyme Inhibitors")) OR (("Schwann Cell Cytoplasm" OR "Schwann Cell  
 Proliferation" OR "Schwann Cell Differentiation") AND "Nerve  
 Degeneration" AND ("Enzyme Activation" OR "Enzyme Inhibitors")) OR  
 (("Schwann Cell Cytoplasm" OR "Schwann Cell Proliferation" OR  
 "Schwann Cell Differentiation") AND "Enzyme Activation" AND ("Enzyme  
 Inhibitors")) OR (("Microglial Cell\*" OR "microglial Activation" OR  
 "microglial Death") AND ("Mitochondrial Dysfunction" OR "mitochondrial  
 Swelling") AND ("Mitogen-Activated Protein Kinase Kinases" OR  
 "Mitogen-Activated Protein Kinases" OR "Glial Fibrillary Acidic Protein"  
 OR (Astrocyte\* AND Reactiv\*) OR "Oxidative Phosphorylation" OR  
 (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme  
 Activation" OR "Enzyme Inhibitors")) OR (("Microglial Cell\*" OR  
 "microglial Activation" OR "microglial Death") AND "Mitogen-Activated  
 Protein Kinase Kinases" AND ("Mitogen-Activated Protein Kinases" OR  
 "Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*) OR  
 "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve  
 Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR  
 (("Microglial Cell\*" OR "microglial Activation" OR "microglial Death")  
 AND "Mitogen-Activated Protein Kinases" AND ("Glial Fibrillary Acidic  
 Protein" OR (Astrocyte\* AND Reactiv\*) OR "Oxidative Phosphorylation"  
 OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme  
 Activation" OR "Enzyme Inhibitors")) OR (("Microglial Cell\*" OR  
 "microglial Activation" OR "microglial Death") AND "Glial Fibrillary  
 Acidic Protein" AND ((Astrocyte\* AND Reactiv\*) OR "Oxidative



Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR (("Microglial Cell\*" OR "microglial Activation" OR "microglial Death") AND (Astrocyte\* AND Reactiv\*) AND ("Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR (("Microglial Cell\*" OR "microglial Activation" OR "microglial Death") AND "Oxidative Phosphorylation" AND ((Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((("Microglial Cell\*" OR "microglial Activation" OR "microglial Death") AND (Caspase-3 AND Activat\*) AND ("Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((("Microglial Cell\*" OR "microglial Activation" OR "microglial Death") AND "Nerve Degeneration" AND ("Enzyme Activation" OR "Enzyme Inhibitors")) OR ((("Microglial Cell\*" OR "microglial Activation" OR "microglial Death") AND "Enzyme Activation" AND ("Enzyme Inhibitors")) OR ((("Mitochondrial Dysfunction" OR "mitochondrial Swelling") AND "Mitogen-Activated Protein Kinase Kinases" AND ("Mitogen-Activated Protein Kinases" OR "Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((("Mitochondrial Dysfunction" OR "mitochondrial Swelling") AND "Mitogen-Activated Protein Kinases" AND ("Glial Fibrillary Acidic Protein" OR (Astrocyte\* AND Reactiv\*) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((("Mitochondrial Dysfunction" OR "mitochondrial Swelling") AND (Astrocyte\* AND Reactiv\*) OR "Oxidative Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((("Mitochondrial Dysfunction" OR "mitochondrial Swelling") AND "Oxidative Phosphorylation" AND ((Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((("Mitochondrial Dysfunction" OR "mitochondrial Swelling") AND (Caspase-3 AND Activat\*) AND ("Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((("Mitochondrial Dysfunction" OR "mitochondrial Swelling") AND "Nerve Degeneration" AND ("Enzyme

Activation" OR "Enzyme Inhibitors")) OR (("Mitochondrial Dysfunction"  
 OR "mitochondrial Swelling") AND "Enzyme Activation" AND ("Enzyme  
 Inhibitors")) OR ("Mitogen-Activated Protein Kinase Kinases" AND  
 "Mitogen-Activated Protein Kinases" AND ("Glial Fibrillary Acidic  
 Protein" OR (Astrocyte\* AND Reactiv\*) OR "Oxidative Phosphorylation"  
 OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme  
 Activation" OR "Enzyme Inhibitors")) OR ("Mitogen-Activated Protein  
 Kinase Kinases" AND "Glial Fibrillary Acidic Protein" AND ((Astrocyte\*  
 AND Reactiv\*) OR "Oxidative Phosphorylation" OR (Caspase-3 AND  
 Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme  
 Inhibitors")) OR ("Mitogen-Activated Protein Kinase Kinases" AND  
 (Astrocyte\* AND Reactiv\*) AND ("Oxidative Phosphorylation" OR  
 (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme  
 Activation" OR "Enzyme Inhibitors")) OR ("Mitogen-Activated Protein  
 Kinase Kinases" AND "Oxidative Phosphorylation" AND ((Caspase-3 AND  
 Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme  
 Inhibitors")) OR ("Mitogen-Activated Protein Kinase Kinases" AND  
 (Caspase-3 AND Activat\*) AND ("Nerve Degeneration" OR "Enzyme  
 Activation" OR "Enzyme Inhibitors")) OR ("Mitogen-Activated Protein  
 Kinase Kinases" AND "Nerve Degeneration" AND ("Enzyme Activation"  
 OR "Enzyme Inhibitors")) OR ("Mitogen-Activated Protein Kinase Kinases"  
 AND "Enzyme Activation" AND ("Enzyme Inhibitors")) OR ("Mitogen-  
 Activated Protein Kinases" AND "Glial Fibrillary Acidic Protein" AND  
 ((Astrocyte\* AND Reactiv\*) OR "Oxidative Phosphorylation" OR  
 (Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme  
 Activation" OR "Enzyme Inhibitors")) OR ("Mitogen-Activated Protein  
 Kinases" AND (Astrocyte\* AND Reactiv\*) AND ("Oxidative  
 Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration"  
 OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ("Mitogen-  
 Activated Protein Kinases" AND "Oxidative Phosphorylation" AND  
 ((Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme  
 Activation" OR "Enzyme Inhibitors")) OR ("Mitogen-Activated Protein  
 Kinases" AND (Caspase-3 AND Activat\*) AND ("Nerve Degeneration" OR  
 "Enzyme Activation" OR "Enzyme Inhibitors")) OR ("Mitogen-Activated  
 Protein Kinases" AND "Nerve Degeneration" AND ("Enzyme Activation"  
 OR "Enzyme Inhibitors")) OR ("Mitogen-Activated Protein Kinases" AND  
 "Enzyme Activation" AND ("Enzyme Inhibitors")) OR ("Glial Fibrillary  
 Acidic Protein" AND (Astrocyte\* AND Reactiv\*) AND ("Oxidative  
 Phosphorylation" OR (Caspase-3 AND Activat\*) OR "Nerve Degeneration"  
 OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ("Glial Fibrillary

Acidic Protein" AND "Oxidative Phosphorylation" AND ((Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ("Glial Fibrillary Acidic Protein" AND (Caspase-3 AND Activat\*) AND ("Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ("Glial Fibrillary Acidic Protein" AND "Nerve Degeneration" AND ("Enzyme Activation" OR "Enzyme Inhibitors")) OR ("Glial Fibrillary Acidic Protein" AND "Enzyme Activation" AND ("Enzyme Inhibitors")) OR ((Astrocyte\* AND Reactiv\*) AND "Oxidative Phosphorylation" AND ((Caspase-3 AND Activat\*) OR "Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Astrocyte\* AND Reactiv\*) AND (Caspase-3 AND Activat\*) AND ("Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Astrocyte\* AND Reactiv\*) AND "Nerve Degeneration" AND ("Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Astrocyte\* AND Reactiv\*) AND "Enzyme Activation" AND ("Enzyme Inhibitors")) OR ("Oxidative Phosphorylation" AND (Caspase-3 AND Activat\*) AND ("Nerve Degeneration" OR "Enzyme Activation" OR "Enzyme Inhibitors")) OR ("Oxidative Phosphorylation" AND "Nerve Degeneration" AND ("Enzyme Activation" OR "Enzyme Inhibitors")) OR ("Oxidative Phosphorylation" AND "Enzyme Activation" AND ("Enzyme Inhibitors")) OR ((Caspase-3 AND Activat\*) AND "Nerve Degeneration" AND ("Enzyme Activation" OR "Enzyme Inhibitors")) OR ((Caspase-3 AND Activat\*) AND "Enzyme Activation" AND ("Enzyme Inhibitors")) OR ("Nerve Degeneration" AND "Enzyme Activation" AND ("Enzyme Inhibitors")) NOT (((demyelinat\* OR remyelinat\* OR "myelin sheath pathology" OR ("myelin sheath" AND (damage OR degenerat\*)) OR "axonal loss" OR "axonal destruction" OR (oligodendrocyte\* AND (APOPTOSIS OR DEATH OR DEGENERAT\* OR DAMAGE OR DYSTROPHY)) OR (oligodendroglia\* AND (apoptosis OR destruct\* OR loss))) OR ("blood-brain barrier" AND (disruption OR "cell adhesion" OR "activated lymphocyte\*" OR "adhesion molecule\*" OR (lymphocyte\* AND trafficking) OR breakdown OR transmigration OR dissolution))) NOT "MULTIPLE SCLEROSIS") OR ("MULTIPLE SCLEROSIS")) AND (PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR FLAVONOIDS OR "DIETARY SUPPLEMENTS")

## **Thrust 2**

(((("Neurodegenerative Disease\*" AND "Reactive Oxygen Species" AND  
 ("Oxidation-Reduction" OR "Hydrogen Peroxide" OR "Oxidative Stress"  
 OR "Free Radicals" OR Antioxidants)) OR ("Neurodegenerative Disease\*" AND  
 "Oxidation-Reduction" AND ("Hydrogen Peroxide" OR "Oxidative Stress" OR  
 "Free Radicals" OR Antioxidants)) OR ("Neurodegenerative Disease\*" AND  
 "Hydrogen Peroxide" AND ("Oxidative Stress" OR "Free Radicals" OR  
 Antioxidants)) OR ("Neurodegenerative Disease\*" AND "Oxidative Stress" AND  
 ("Free Radicals" OR Antioxidants)) OR ("Neurodegenerative Disease\*" AND  
 "Free Radicals" AND Antioxidants) OR ("Reactive Oxygen Species" AND  
 "Oxidation-Reduction" AND ("Hydrogen Peroxide" OR "Oxidative Stress" OR  
 "Free Radicals" OR Antioxidants)) OR ("Reactive Oxygen Species" AND  
 "Hydrogen Peroxide" AND ("Oxidative Stress" OR "Free Radicals" OR  
 Antioxidants)) OR ("Reactive Oxygen Species" AND "Oxidative Stress" AND  
 ("Free Radicals" OR Antioxidants)) OR ("Reactive Oxygen Species" AND  
 "Free Radicals" AND Antioxidants) OR ("Oxidation-Reduction" AND  
 "Hydrogen Peroxide" AND ("Oxidative Stress" OR "Free Radicals" OR  
 Antioxidants)) OR ("Oxidation-Reduction" AND "Oxidative Stress" AND  
 ("Free Radicals" OR Antioxidants)) OR ("Oxidation-Reduction" AND  
 "Free Radicals" AND Antioxidants) OR ("Hydrogen Peroxide" AND  
 "Oxidative Stress" AND ("Free Radicals" OR Antioxidants)) OR  
 ("Hydrogen Peroxide" AND "Free Radicals" AND Antioxidants) OR  
 ("Oxidative Stress" AND "Free Radicals" AND Antioxidants)) NOT  
 (((((demyelinat\* OR remyelinat\* OR "myelin sheath pathology" OR  
 ("myelin sheath" AND (damage OR degenerat\*)) OR "axonal loss" OR  
 "axonal destruction" OR (oligodendrocyte\* AND (APOPTOSIS OR DEATH OR  
 DEGENERAT\* OR DAMAGE OR DYSTROPHY)) OR (oligodendroglia\* AND  
 (apoptosis OR destruct\* OR loss))) OR ("blood-brain barrier" AND  
 (disruption OR "cell adhesion" OR "activated lymphocyte\*" OR  
 "adhesion molecule\*" OR (lymphocyte\* AND trafficking) OR  
 breakdown OR transmigration OR dissolution))) NOT "MULTIPLE  
 SCLEROSIS") OR ("MULTIPLE SCLEROSIS")) AND (PLANTS, MEDICINAL OR  
 PLANTS, EDIBLE OR "PLANT EXTRACTS" OR "PLANT PREPARATIONS" OR  
 "PLANT OILS" OR PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS"  
 OR ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR FLAVONOIDS  
 OR "DIETARY SUPPLEMENTS")

### **Thrust 3**

((("Cell Membrane Permeability" AND "Active Biological Transport") OR ("Cell Membrane Permeability" AND "Endothelial Growth Factor\*") OR ("Cell Membrane Permeability" AND "Cell Surface receptors") OR ("Cell Membrane Permeability" AND "Capillary Permeability") OR ("Cell Membrane Permeability" AND "Blood-Brain Barrier") OR ("Cell Membrane Permeability" AND "Carrier Protein\*") OR ("Cell Membrane Permeability" AND "Tight Junction\*") OR ("Active Biological Transport" AND "Endothelial Growth Factor\*") OR ("Active Biological Transport" AND "Cell Surface receptors") OR ("Active Biological Transport" AND "Capillary Permeability") OR ("Active Biological Transport" AND "Blood-Brain Barrier") OR ("Active Biological Transport" AND "Carrier Protein\*") OR ("Active Biological Transport" AND "Tight Junction\*") OR ("Endothelial Growth Factor\*" AND "Cell Surface receptors") OR ("Endothelial Growth Factor\*" AND "Capillary Permeability") OR ("Endothelial Growth Factor\*" AND "Blood-Brain Barrier") OR ("Endothelial Growth Factor\*" AND "Carrier Protein\*") OR ("Endothelial Growth Factor\*" AND "Tight Junction\*") OR ("Cell Surface receptors" AND "Capillary Permeability") OR ("Cell Surface receptors" AND "Blood-Brain Barrier") OR ("Cell Surface receptors" AND "Carrier Protein\*") OR ("Cell Surface receptors" AND "Tight Junction\*") OR ("Capillary Permeability" AND "Blood-Brain Barrier") OR ("Capillary Permeability" AND "Carrier Protein\*") OR ("Capillary Permeability" AND "Tight Junction\*") OR ("Blood-Brain Barrier" AND "Carrier Protein\*") OR ("Blood-Brain Barrier" AND "Tight Junction\*") OR ("Carrier Protein\*" AND "Tight Junction\*")) NOT (((demyelinat\* OR remyelinat\* OR "myelin sheath pathology" OR ("myelin sheath" AND (damage OR degenerat\*)) OR "axonal loss" OR "axonal destruction" OR (oligodendrocyte\* AND (APOPTOSIS OR DEATH OR DEGENERAT\* OR DAMAGE OR DYSTROPHY)) OR (oligodendroglia\* AND (apoptosis OR destruct\* OR loss))) OR ("blood-brain barrier" AND (disruption OR "cell adhesion" OR "activated lymphocyte\*" OR "adhesion molecule\*" OR (lymphocyte\* AND trafficking) OR breakdown OR transmigration OR dissolution))) NOT "MULTIPLE SCLEROSIS") OR ("MULTIPLE SCLEROSIS")) AND (PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR FLAVONOIDS OR "DIETARY SUPPLEMENTS")

#### **Thrust 4**

((("Tumor Necrosis Factor receptor\*" AND "recombinant Interferon Gamma") OR ("Tumor Necrosis Factor receptor\*" AND "Inflammatory Response") OR ("Tumor Necrosis Factor receptor\*" AND "Inflammatory Cytokine\*") OR ("Tumor Necrosis Factor receptor\*" AND "Activated Macrophage\*") OR ("Tumor Necrosis Factor receptor\*" AND "Macrophage Infiltration") OR ("Tumor Necrosis Factor receptor\*" AND "Interferon Type II") OR ("recombinant Interferon Gamma" AND "Inflammatory Response") OR ("recombinant Interferon Gamma" AND "Inflammatory Cytokine\*") OR ("recombinant Interferon Gamma" AND "Activated Macrophage\*") OR ("recombinant Interferon Gamma" AND "Macrophage Infiltration") OR ("recombinant Interferon Gamma" AND "Interferon Type II") OR ("Inflammatory Response" AND "Inflammatory Cytokine\*") OR ("Inflammatory Response" AND "Activated Macrophage\*") OR ("Inflammatory Response" AND "Macrophage Infiltration") OR ("Inflammatory Response" AND "Interferon Type II") OR ("Inflammatory Cytokine\*" AND "Activated Macrophage\*") OR ("Inflammatory Cytokine\*" AND "Macrophage Infiltration") OR ("Inflammatory Cytokine\*" AND "Interferon Type II") OR ("Activated Macrophage\*" AND "Macrophage Infiltration") OR ("Activated Macrophage\*" AND "Interferon Type II") OR ("Macrophage Infiltration" AND "Interferon Type II")) NOT (((demyelinat\* OR remyelinat\* OR "myelin sheath pathology" OR ("myelin sheath" AND (damage OR degenerat\*)) OR "axonal loss" OR "axonal destruction" OR (oligodendrocyte\* AND (APOPTOSIS OR DEATH OR DEGENERAT\* OR DAMAGE OR DYSTROPHY)) OR (oligodendroglia\* AND (apoptosis OR destruct\* OR loss))) OR ("blood-brain barrier" AND (disruption OR "cell adhesion" OR "activated lymphocyte\*" OR "adhesion molecule\*" OR (lymphocyte\* AND trafficking) OR breakdown OR transmigration OR dissolution))) NOT "MULTIPLE SCLEROSIS") OR ("MULTIPLE SCLEROSIS")) AND (PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR FLAVONOIDS OR "DIETARY SUPPLEMENTS")

#### **Thrust 5 --- combo of 3**

(((("Myelin Basic Protein\*" AND Immunology) AND ("Peptide Fragment\*" AND Immunology) AND ("Major Histocompatibility Complex" OR "CD4 Positive T-Lymphocyte\*" OR "CD8 Positive T-Lymphocyte\*" OR (Antigens AND Immunology) OR "Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Myelin Basic Protein\*" AND Immunology) AND "Major Histocompatibility Complex" AND ("CD4 Positive T-Lymphocyte\*" OR "CD8 Positive T-Lymphocyte\*" OR (Antigens AND Immunology) OR "Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Myelin Basic Protein\*" AND Immunology) AND "CD4 Positive T-Lymphocyte\*" AND ("CD8 Positive T-Lymphocyte\*" OR (Antigens AND Immunology) OR "Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Myelin Basic Protein\*" AND Immunology) AND "CD8 Positive T-Lymphocyte\*" AND ((Antigens AND Immunology) OR "Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Myelin Basic Protein\*" AND Immunology) AND (Antigens AND Immunology) AND ("Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Myelin Basic Protein\*" AND Immunology) AND "Blood Mononuclear Cell\*" AND ("Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Myelin Basic Protein\*" AND Immunology) AND "Leukocyte Chemotaxis" AND Immunophenotyping) OR (("Peptide Fragment\*" AND Immunology) AND "Major Histocompatibility Complex" AND ("CD4 Positive T-Lymphocyte\*" OR "CD8 Positive T-Lymphocyte\*" OR (Antigens AND Immunology) OR "Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Peptide Fragment\*" AND Immunology) AND "CD4 Positive T-Lymphocyte\*" AND ("CD8 Positive T-Lymphocyte\*" OR (Antigens AND Immunology) OR "Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Peptide Fragment\*" AND Immunology) AND "CD8 Positive T-Lymphocyte\*" AND ((Antigens AND Immunology) OR "Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Peptide Fragment\*" AND Immunology) AND (Antigens AND Immunology) AND ("Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Peptide Fragment\*" AND Immunology) AND "Blood Mononuclear Cell\*" AND ("Leukocyte Chemotaxis" OR Immunophenotyping)) OR (("Peptide Fragment\*" AND Immunology) AND "Leukocyte Chemotaxis" AND Immunophenotyping) OR ("Major Histocompatibility Complex" AND "CD4 Positive T-Lymphocyte\*" AND

("CD8 Positive T-Lymphocyte\*" OR (Antigens AND Immunology) OR  
 "Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR  
 Immunophenotyping)) OR ("Major Histocompatibility Complex" AND  
 "CD8 Positive T-Lymphocyte\*" AND ((Antigens AND Immunology) OR  
 "Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR  
 Immunophenotyping)) OR ("Major Histocompatibility Complex" AND  
 (Antigens AND Immunology) AND ("Blood Mononuclear Cell\*" OR  
 "Leukocyte Chemotaxis" OR Immunophenotyping)) OR ("Major  
 Histocompatibility Complex" AND "Blood Mononuclear Cell\*" AND  
 ("Leukocyte Chemotaxis" OR Immunophenotyping)) OR ("Major  
 Histocompatibility Complex" AND "Leukocyte Chemotaxis" AND  
 Immunophenotyping) OR ("CD4 Positive T-Lymphocyte\*" AND "CD8  
 Positive T-Lymphocyte\*" AND ((Antigens AND Immunology) OR "Blood  
 Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR  
 Immunophenotyping)) OR ("CD4 Positive T-Lymphocyte\*" AND (Antigens  
 AND Immunology) AND ("Blood Mononuclear Cell\*" OR "Leukocyte  
 Chemotaxis" OR Immunophenotyping)) OR ("CD4 Positive T-  
 Lymphocyte\*" AND "Blood Mononuclear Cell\*" AND ("Leukocyte  
 Chemotaxis" OR Immunophenotyping)) OR ("CD4 Positive T-  
 Lymphocyte\*" AND "Leukocyte Chemotaxis" AND Immunophenotyping)  
 OR ("CD8 Positive T-Lymphocyte\*" AND (Antigens AND Immunology)  
 AND ("Blood Mononuclear Cell\*" OR "Leukocyte Chemotaxis" OR  
 Immunophenotyping)) OR ("CD8 Positive T-Lymphocyte\*" AND "Blood  
 Mononuclear Cell\*" AND ("Leukocyte Chemotaxis" OR  
 Immunophenotyping)) OR ("CD8 Positive T-Lymphocyte\*" AND  
 "Leukocyte Chemotaxis" AND Immunophenotyping) OR ((Antigens AND  
 Immunology) AND "Blood Mononuclear Cell\*" AND ("Leukocyte  
 Chemotaxis" OR Immunophenotyping)) OR ((Antigens AND Immunology)  
 AND "Leukocyte Chemotaxis" AND Immunophenotyping) OR ("Blood  
 Mononuclear Cell\*" AND "Leukocyte Chemotaxis" AND  
 Immunophenotyping)) NOT (((demyelinat\* OR remyelinat\* OR "myelin  
 sheath pathology" OR ("myelin sheath" AND (damage OR degenerat\*)) OR  
 "axonal loss" OR "axonal destruction" OR (oligodendrocyte\* AND  
 (APOPTOSIS OR DEATH OR DEGENERAT\* OR DAMAGE OR  
 DYSTROPHY)) OR (oligodendroglia\* AND (apoptosis OR destruct\* OR  
 loss))) OR ("blood-brain barrier" AND (disruption OR "cell adhesion" OR  
 "activated lymphocyte\*" OR "adhesion molecule\*" OR (lymphocyte\* AND  
 trafficking) OR breakdown OR transmigration OR dissolution))) NOT  
 "MULTIPLE SCLEROSIS") OR ("MULTIPLE SCLEROSIS")) AND  
 (PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT



EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR FLAVONOIDS OR "DIETARY SUPPLEMENTS")

**Thrust 5 --- combo of 2**

(((((“Myelin Basic Protein” AND Immunology) AND (“Peptide Fragment\*” AND Immunology)) OR ((“Myelin Basic Protein” AND Immunology) AND “Major Histocompatibility Complex”) OR ((“Myelin Basic Protein” AND Immunology) AND “CD4 Positive T-Lymphocyte\*”) OR ((“Myelin Basic Protein” AND Immunology) AND “CD8 Positive T-Lymphocyte\*”) OR ((“Myelin Basic Protein” AND Immunology) AND (Antigens AND Immunology)) OR ((“Myelin Basic Protein” AND Immunology) AND “Blood Mononuclear Cell\*”) OR ((“Myelin Basic Protein” AND Immunology) AND “Leukocyte Chemotaxis”) OR ((“Myelin Basic Protein” AND Immunology) AND Immunophenotyping) OR ((“Peptide Fragment\*” AND Immunology) AND “Major Histocompatibility Complex”) OR ((“Peptide Fragment\*” AND Immunology) AND “CD4 Positive T-Lymphocyte\*”) OR ((“Peptide Fragment\*” AND Immunology) AND “CD8 Positive T-Lymphocyte\*”) OR ((“Peptide Fragment\*” AND Immunology) AND (Antigens AND Immunology)) OR ((“Peptide Fragment\*” AND Immunology) AND “Blood Mononuclear Cell\*”) OR ((“Peptide Fragment\*” AND Immunology) AND “Leukocyte Chemotaxis”) OR ((“Peptide Fragment\*” AND Immunology) AND Immunophenotyping) OR (“Major Histocompatibility Complex” AND “CD4 Positive T-Lymphocyte\*”) OR (“Major Histocompatibility Complex” AND “CD8 Positive T-Lymphocyte\*”) OR (“Major Histocompatibility Complex” AND (Antigens AND Immunology)) OR (“Major Histocompatibility Complex” AND “Blood Mononuclear Cell\*”) OR (“Major Histocompatibility Complex” AND “Leukocyte Chemotaxis”) OR (“Major Histocompatibility Complex” AND Immunophenotyping) OR (“CD4 Positive T-Lymphocyte\*” AND “CD8 Positive T-Lymphocyte\*”) OR (“CD4 Positive T-Lymphocyte\*” AND (Antigens AND Immunology)) OR (“CD4 Positive T-Lymphocyte\*” AND “Blood Mononuclear Cell\*”) OR (“CD4 Positive T-Lymphocyte\*” AND “Leukocyte Chemotaxis”) OR (“CD4 Positive T-Lymphocyte\*” AND Immunophenotyping) OR (“CD8 Positive T-Lymphocyte\*” AND (Antigens AND Immunology)) OR (“CD8 Positive T-Lymphocyte\*” AND “Blood Mononuclear Cell\*”) OR (“CD8 Positive T-Lymphocyte\*” AND

“Leukocyte Chemotaxis”) OR (“CD8 Positive T-Lymphocyte\*” AND Immunophenotyping) OR ((Antigens AND Immunology) AND “Blood Mononuclear Cell\*”) OR ((Antigens AND Immunology) AND “Leukocyte Chemotaxis”) OR ((Antigens AND Immunology) AND Immunophenotyping) OR (“Blood Mononuclear Cell\*” AND “Leukocyte Chemotaxis”) OR (“Blood Mononuclear Cell\*” AND Immunophenotyping) OR (“Leukocyte Chemotaxis” AND Immunophenotyping)) NOT (((demyelinat\* OR remyelinat\* OR "myelin sheath pathology" OR ("myelin sheath" AND (damage OR degenerat\*)) OR "axonal loss" OR "axonal destruction" OR (oligodendrocyte\* AND (APOPTOSIS OR DEATH OR DEGENERAT\* OR DAMAGE OR DYSTROPHY)) OR (oligodendroglia\* AND (apoptosis OR destruct\* OR loss))) OR ("blood-brain barrier" AND (disruption OR "cell adhesion" OR "activated lymphocyte\*" OR "adhesion molecule\*" OR (lymphocyte\* AND trafficking) OR breakdown OR transmigration OR dissolution))) NOT "MULTIPLE SCLEROSIS") OR ("MULTIPLE SCLEROSIS")) AND (PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR FLAVONOIDS OR "DIETARY SUPPLEMENTS")

## APPENDIX 4 – SYNERGIES IDENTIFIED IN PRESENT STUDY

1. “Periodic slit-lamp microscope examination indicated that in combination with vitamin-E, 0.01% curcumin (G-IV) delayed the onset and maturation of galactose-induced cataract. Biochemical analyses revealed that combined treatment of 0.01% *curcumin and vitamin-E diet* exhibited an efficient antioxidant effect, as it inhibited lipid peroxidation and contributed to a distinct rise in reduced glutathione content. The results indicate that *natural dietary ingredients are effective in combination rather than the individual administration as they are complementing each other in reducing the risk of galactose induced cataract.*” [14]

[This again validates our thesis that combinations of potential discoveries may also be considered as a discovery, and that the concept of an anti-cataract lifestyle, where multiple ‘discoveries’ are utilized, may be the real key to improving cataracts.]

2.. “Regular consumption of fruit and vegetables is associated with reduced risks of cancer, cardiovascular disease, stroke, Alzheimer disease, cataracts, and some of the functional declines associated with aging.....We propose that the *additive and synergistic effects of phytochemicals in fruit and vegetables are responsible for their potent antioxidant and anticancer activities, and that the benefit of a diet rich in fruit and vegetables is attributed to the complex mixture of phytochemicals present in whole foods.*” [15]

[Further validation of the combination thesis].

3. “From a disease-prevention perspective, recent progress in phytochemical and nutraceutical research clearly suggests benefits outweigh the risk pattern. Although powerful antioxidant properties have been the most acclaimed mechanism of action for these entities, the individual antioxidants studied in clinical trials do not appear to have consistent preventative effects. The actions of the antioxidant nutrients alone do not explain the observed health benefits of diets rich in fruits and vegetables for chronic diseases. .... our investigation suggests that a *mixture containing an assortment of phytochemicals/nutraceuticals may serve as a much more powerful blend in preventing drug or chemical-induced organ injuries than a single phytochemical or nutraceutical entity.*” [16]

[The importance of this article is that it shows the combination of known anti-oxidants provides a synergistic, more predictable effect.

**This validates our thesis that combinations of potential discoveries may also be considered as a discovery]**

## **APPENDIX 5 – SYNERGIES IDENTIFIED IN OTHER MEDICAL AREAS**

“Autoantibodies to citrullinated telopeptides of type I and II collagen and to CCPs [cyclic citrullinated peptides] exert a synergistic effect on the risk of seropositive RA [Rheumatoid Arthritis]. [17].

“The synergistic effects of *Lactobacillus rhamnosus* and bovine colostrums on the immunity of mice in vivo and in vitro were investigated..... *L. rhamnosus* and bovine colostrums can enhance the functions of immune system supported by lymphocytes and peritoneal macrophages either in vivo or in vitro”. [18].

“We investigated the effect of dietary genistein (the principal soy isoflavone) alone and combined with L-carnitine to evaluate possible synergistic effects on the intentionally induced prediabetic state characterized by insulin resistance and obesity in C57Bl/6J mice fed a high-fat diet (HD)..... Our study suggests that genistein with carnitine exerts anti-obesity effects, probably by modulating peroxisome proliferator-activated receptor-associated genes.” [19].

“These results suggested that vitamin E and selenium have synergistic effects on immune responses.” [20].

“...the synergistic effects of CR [caloric restriction] with maintained protein intake may help to limit the progression of sarcopenia by optimizing the turnover rates and functions of major proteins in skeletal muscle.” [21].

“Catechins belong to a large group of polyphenolic compounds that are ubiquitous in tea leaves..... Their antioxidant activity is enhanced by the synergistic action between catechins, e.g. EGCG, EGC, ECG, EC, pheophytins a and b, and other components in tea leaves.” [22].

“Intake of some dietary items may modify the effect of others. An analysis framework explicitly recognizing complementary and potentially synergistic effects of food, drinks, and smoking could enhance our understanding of dietary epidemiology.” [23].

“alpha-Lipoic acid (ALA) and vitamin E (VE) have synergistic effects, as determined in models of oxidant radical lesions. This review summarizes

recent findings showing that the combination of ALA plus VE has beneficial effects in reducing oxidative damage in ischemic or other oxidation-related pathologic events. Both antioxidants are common in the normal human diet, and side effects are very rare. Therefore, ALA and VE can counteract oxidative processes and could have an important role in clinical medicine.” [24].

“Taking into account the manifold possible synergies for inhibition of starch, protein and/ or lipid digestion by the spectrum of polyphenol components present within berry species, the inhibition of digestive enzymes by dietary polyphenols may represent an under- reported mechanism for delivering some of the health benefits attributed to a diet rich in fruit and vegetables.” [25].

“The different types of fructans studied in the present experiment seem to have similar activity on mineral absorption. However, the combination of OF and HP-inulin showed synergistic effects on intestinal Ca absorption and balance in rats.” [26].

“MMF [mycophenolate mofetil] treatment decreases CsA-induced nephrotoxicity, and combined treatment with LSRT [losartan] has a synergistic effect in preventing chronic CsA nephrotoxicity.” [27].

“The combination of SPC and black tea synergistically inhibited prostate tumorigenicity, final tumor weight and metastases to lymph nodes in vivo. The combination of SPC and green tea synergistically inhibited final tumor weight and metastasis and significantly reduced serum concentrations of both testosterone and DHT in vivo.” [28].

“A higher intake of either linolenic or linoleic acid was inversely related to the prevalence odds ratio of CAD [coronary artery disease]. The 2 fatty acids had synergistic effects on the prevalence odds ratio of CAD.” [29].

“In conclusion, a combination of different carbohydrates showed synergistic effects on intestinal Ca absorption and balance in rats. Further studies with other types of carbohydrate combinations should be carried out to extend these findings.” [30].

“...curcuminoids and sesquiterpenoids in turmeric exhibit hypoglycemic effects via PPAR-gamma activation as one of the mechanisms, and suggest

that E-ext (ethanol extraction) including curcuminoids and sesquiterpenoids has the additive or synergistic effects of both components.” [31].

“Treatment with both ZD55-MnSOD and 5-FU could induce more significant apoptosis in cancer cells compared with ZD55-MnSOD or 5-FU alone, respectively. A better antitumor activity was observed by ZD55-MnSOD plus 5-fluorouracil (5-FU) treatment. Tumor growth was greatly inhibited by this combined treatment, and animal survival time increased.....These results show that, by using the combination therapies, a significant decrease in tumor mass can be achieved, which suggest that ZD55-MnSOD in combination with 5-FU may have potential clinical implications.” [32].

“The study indicates that galantamine and risperidone may have synergistic effect on the cognitive impairments in schizophrenia patients by synergistically promoting the nAChR activation-dependent increase of dopamine D(1) receptor-mediated neurotransmission.” [33].

The observed significant synergistic effect of BPb and blood cadmium on increasing serum testosterone, and additive effect of a decrease in serum selenium on increasing serum testosterone, may have implications on the initiation and development of prostate cancer because testosterone augments the progress of prostate cancer in its early stages. [34].

The objective of this study was to examine the effects of cell-adhesion peptides incorporated into collagen scaffolds on corneal epithelial cell stratification..... A synergistic effect of the combined sequences from laminin was observed, with the orientation of the peptide sequences having a great impact on the ability of the materials to promote cell stratification. [35].

Although, there were only two genes, pe38 and orf17, that were activated by IE2, we discovered interestingly that the combination of IE1 and IE2 factors had a synergistic effect on activation of the AcMNPV genome in mammalian cells, and activated around 38 %, or 59 out of the 155 genes placed on the microarray. This is the first detailed study of baculoviral transcription regulation in mammalian cells, and it shows that the baculoviral genome can be activated in a mammalian system, and also that the two major trans-activators, IE1 and IE2, play a central role in this activation. [36].

“The aim of the present study was to evaluate a possible interaction between R219K polymorphism of ABCA1 gene and G > C polymorphism in intron 7 of PPARA gene in determining the risk of the CAD [coronary artery disease]..... The synergy index value equals 3.98 and indicates a quite strong synergistic effect between the analysed polymorphisms.....The present study shows that R219K polymorphism of ABCA1 gene and G > C polymorphism in intron 7 of PPARA gene act cumulatively and synergistically in determining the risk of premature CAD.” [37].

“We identified a new vaccine adjuvant, a local combination of GM-CSF and IL-2, which is synergistic in enhancing peptide specific immune response through local effect without increasing T(reg) cells. This immune response was found to be long lasting and protective in tumor bearing mice.” [38].

“...enriched tumor-bearing mice had statistically significant prolonged survival, with 44% of them disease-free compared with 0% in the standard rearing tumor-bearing mice. The possible mechanisms for the enhancement of immunotherapy by environmental enrichment are cognitive, physical activity, and psychologic. The demonstration of synergistic effect of cancer therapy and environmental enrichment on tumor rejection has important implication for cancer treatment.” [39].

“The combinational use of acyclovir (ACV) phosphonate esters and alpha(2)-interferon was shown to produce a synergistic effect on inhibition of HSV-1 replication in Vero cell cultures.” [40].

“Carotenoids are compounds contained in foods and possess anticarcinogenic activity. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising candidate for cancer therapeutics due to its ability to induce apoptosis selectively in cancer cells. However, some tumors remain tolerant to TRAIL-induced apoptosis..... These results indicate that the combination of certain carotenoids and TRAIL is a new strategy to overcome TRAIL resistance in cancer cells.” [41].



## **APPENDIX 6 – TAXONOMY OF PARKINSON'S DISEASE CORE LITERATURE**

This appendix provides a taxonomy of the PD core literature restricted to select semantic classes, and provides a brief analysis of each cluster. While this is not discovery, since PD is mentioned in each record, nevertheless, there is substantial value in collecting this information in one place.

The query used to retrieve the PD core literature was restricted to non-drug semantic classes, similar conceptually to what was used in Chapter 5. The main difference is that the query used for this appendix contained more non-drug semantic classes than was the case for Chapter 5. This larger query may be written as:

(PLANTS, MEDICINAL OR PLANTS, EDIBLE OR "PLANT EXTRACTS" OR "PLANT PREPARATIONS" OR "PLANT OILS" OR PHYTOTHERAPY OR FRUIT OR VEGETABLES OR "FISH OILS" OR ALGAE OR NUTS OR "DAIRY PRODUCTS" OR FATS OR DIET OR FLAVONOIDS OR "DIETARY SUPPLEMENTS" OR Plants OR Chimera OR Organisms, Genetically Modified OR Plankton OR Plant Components OR Plant Families and Groups OR Plants, Toxic OR Seedling OR Trees OR Algae OR Algae, Brown OR Algae, Golden-Brown OR Algae, Green OR Algae, Red OR Characeae OR Cryptophyta OR Cyanophora OR Euglenida OR Lichens OR Oomycetes OR Seaweed) AND (PARKINSON\* NOT (PARKINSON [AU] OR PARKINSONIA OR WOLFF-PARKINSON))

where the phrases in CAPS are those used in the Chapter 5 core query, and the lower case phrases are those added for this appendix. There are undoubtedly more non-drug semantic classes that could be added, but we believe the present query provides a good representation of the total core PD non-drug literature.

We entered the query into the PubMed search engine, and retrieved 1367 records with Abstracts. We then clustered these records into sixteen elemental clusters, using our CLUTO document clustering algorithm. Since we used non-fuzzy clustering (each record assigned to one cluster only), where multi-theme records are not exploited fully in the display, we recommend anyone searching for interesting findings examine all the clusters listed.

## Taxonomy

There are two main taxonomy categories: Clinical and Epidemiological Studies (468 records), and Laboratory Research Studies (899 records). The contents of each cluster in these two groupings will now be presented. The format for each cluster is a short summary of the theme, followed by key weighted phrases from the records in the cluster, followed by titles of the records contained within the cluster. The reader interested in more details about a specific record should enter some or all of the title into PubMed (or any Medline search engine) and retrieve the Abstract.

## CLINICAL AND EPIDEMIOLOGICAL STUDIES

### **Cluster 1 – Levodopa and Dietary Treatment**

levodopa 19.4%, dopa 12.1%, diet 6.8%, patient 6.4%, fluctuat 3.2%, plasma 2.5%, protein.diet 1.5%, carbidopa 1.2%, low.protein 1.2%, protein 1.1%, low 1.1%, patients.parkinson 1.0%, mucuna 1.0%, lnaa 0.9%, sinemet 0.8%, intak 0.8%, patients.parkinson.disease 0.7%, respons 0.7%, prurien 0.7%, mucuna.pruriens 0.6%

Effects of Mucuna pruriens extract on activation of prothrombin by Echis carinatus venom.

[Diet in Parkinson disease]

Aluminum decreases the magnesium concentration of spinal cord and trabecular bone in rats fed a low calcium, high aluminum diet.

[Similarities in calcium and magnesium metabolism between amyotrophic lateral sclerosis and calcification of the spinal cord in the Kii Peninsula ALS focus]

[Pharmacological therapy of complicated Parkinson's disease]

[The effect of controlled release of DOPA and carbidopa on clinical response and plasma pharmacokinetics of DOPA in parkinsonian patients]

Effects of low calcium and magnesium dietary intake on the central nervous system tissues of rats and calcium-magnesium related disorders in the amyotrophic lateral sclerosis focus in the Kii Peninsula of Japan.

An alternative medicine treatment for Parkinson's disease: results of a multicenter clinical trial. HP-200 in Parkinson's Disease Study Group.

[Diet therapy in Parkinson disease]

Effects of calcium-deficient diets on manganese deposition in the central nervous system and bones of rats.

Dietary factors in the management of Parkinson's disease.

Mucuna pruriens: improvement of the biotechnological production of the anti-Parkinson drug L-dopa by plant cell selection.

[Efficacy of the proteic redistribution diet (PRD) in the antiparkinsonian effect of L-dopa]

Broad bean (*Vicia faba*) consumption and Parkinson's disease.

Clinical and pharmacokinetic effects of a diet rich in insoluble fiber on Parkinson disease.

[Influence of protein-restricted diet on motor response fluctuations in Parkinson's disease]

Improvement of parkinsonian features correlate with high plasma levodopa values after broad bean (*Vicia faba*) consumption.

Effect of daytime protein restriction on nutrient intakes of free-living Parkinson's disease patients.

Protein redistribution diet remains effective in patients with fluctuating parkinsonism.

[Effect of a controlled low-protein diet on the pharmacological response to levodopa and on the plasma levels of L-dopa and amino acids in patients with Parkinson's disease]

A balanced carbohydrate: protein diet in the management of Parkinson's disease.

Dietary modification of Parkinson's disease.

The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers.

Standard and controlled-release levodopa/carbidopa in patients with fluctuating Parkinson's disease on a protein redistribution diet. A preliminary report.

Protein redistribution diet and antiparkinsonian response to levodopa.

[Proposal for a protein redistribution diet in the control of motor fluctuations in Parkinson's disease: acceptance and efficacy]

Predicting beneficial response to a protein-redistribution diet in fluctuating Parkinson's disease.

Diurnal differences in response to oral levodopa.

New concepts in the treatment of Parkinson's disease.

Paralysis agitans and levodopa in "Ayurveda": ancient Indian medical treatise.

Pharmacokinetics and bioavailability of Sinemet CR: a summary of human studies.

Influence of fluctuations of plasma large neutral amino acids with normal diets on the clinical response to levodopa.

Amount and distribution of dietary protein affects clinical response to levodopa in Parkinson's disease.

The effect of dietary protein on the efficacy of L-dopa: a double-blind study.

'On-off' phenomenon in Parkinson's disease: relationship between dopa and other large neutral amino acids in plasma.

Practical application of a low-protein diet for Parkinson's disease.

Protein redistribution diet restores motor function in patients with dopa-resistant "off" periods.

Plasma levels of amino acids correlate with motor fluctuations in parkinsonism.

Influence of dietary protein on motor fluctuations in Parkinson's disease.

Dietary method for reducing fluctuations in Parkinson's disease.

Behavioural and biochemical changes following chronic administration of L-dopa to rats.

Deprenyl administration in man: a selective monoamine oxidase B inhibitor without the 'cheese effect'.

[The "off-on" phenomenon during treatment of parkinson's disease with levodopa (author's transl)]

Effect of L-DOPA on endogenous histamine metabolism.

Decrease of the 3,4-dihydroxyphenylalanine (DOPA) decarboxylase activities in human erythrocytes and mouse tissues after administration of DOPA.

Pharmacokinetics of L-dopa : Special reference to food and aging.

Special low-protein foods ameliorate postprandial off in patients with advanced Parkinson's disease.

Protein intake in Parkinsonian patients using the EPIC food frequency questionnaire.

Low plasma uric acid level in Parkinson's disease.

[Inter- and intraindividual pharmacokinetic variations in the treatment of Parkinson's disease]

Postmortem brain fatty acid profile of levodopa-treated Parkinson disease patients and parkinsonian monkeys.

Docosahexaenoic acid reduces levodopa-induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys.

Banana juice reduces bioavailability of levodopa preparation.

Hydrosoluble fiber (*Plantago ovata* husk) and levodopa II: experimental study of the pharmacokinetic interaction in the presence of carbidopa.

Hydrosoluble fiber (*Plantago ovata* husk) and levodopa I: experimental study of the pharmacokinetic interaction.

Extraction of bioactive principles from *Mucuna pruriens* seeds.

The anti-Parkinson drug budipine is exported actively out of the brain by P-glycoprotein in mice.

Hyperhomocysteinemia in L-dopa treated Parkinson's disease patients: effect of cobalamin and folate administration.

Effects of subthalamic nucleus deep brain stimulation and levodopa on energy production rate and substrate oxidation in Parkinson's disease.

Case of neuroleptic malignant-like syndrome precipitated by abrupt fava bean discontinuance.

*Mucuna pruriens* in Parkinson's disease: a double blind clinical and pharmacological study.

Neuroprotective effects of the antiparkinson drug *Mucuna pruriens*.

The effects of a normal protein diet on levodopa plasma kinetics in advanced Parkinson's disease.

Effect of antiparkinson drug HP-200 (*Mucuna pruriens*) on the central monoaminergic neurotransmitters.

Experimental study on inhibition of neuronal toxic effect of levodopa by ginkgo biloba extract on Parkinson disease in rats.

Quercetin potentiates L-Dopa reversal of drug-induced catalepsy in rats: possible COMT/MAO inhibition.

[Effect of bushen yanggan recipe on nigrostriatal function in parkinsonian model rats after long-term levodopa treatment]

L-DOPA: from a biologically inactive amino acid to a successful therapeutic agent.

## **Cluster 2 – Nutritional and Limited Drug Therapies**

patient 16.1%, treatment 2.4%, drug 2.1%, therapi 2.0%, nutrit 1.9%, symptom 1.7%, medic 1.4%, weight 1.3%, diagnosi 1.3%, dose 1.2%, psp 1.0%, clinic 1.0%, scale 0.9%, control 0.8%, selegilin 0.7%, rate 0.6%, constip 0.6%, syndrom 0.6%, disord 0.6%, diet 0.6%

REM sleep behavior disorder in patients with guadeloupean parkinsonism, a tauopathy.

Interactions between herbal medicines and prescribed drugs: a systematic review.

Warfarin and ropinirole interaction.

The use of alternative therapies by patients with Parkinson's disease.

Epidemiology of progressive supranuclear palsy. ESGAP Consortium.  
European Study Group on Atypical Parkinsonisms.

[Evaluation of a dessert in patients with deglutition changes, one more step in advanced basic feeding]

[Psychiatric comorbidity in somatic disorders. Psychophytopharmaceuticals are worth a try]

Seeing trees but not the forest: limited perception of large configurations in PD.

Ruscus aculeatus (butcher's broom) as a potential treatment for orthostatic hypotension, with a case report.

Bromocriptine improves glycaemic control and serum lipid profile in obese Type 2 diabetic subjects: a new approach in the treatment of diabetes.

Mechanisms of body weight gain in patients with Parkinson's disease after subthalamic stimulation.

The parkinsonian models: invertebrates to mammals.



The effects of the traditional chinese medicine, "Banxia Houpo Tang (Hange-Koboku To)" on the swallowing reflex in Parkinson's disease.

Association of L-DOPA with recovery following Ayurveda medication in Parkinson's disease.

Cytochrome P450-dependent N-dealkylation of L-deprenyl in C57BL mouse liver microsomes: effects of in vivo pretreatment with ethanol, phenobarbital, beta-naphthoflavone and L-deprenyl.

Cannabis in movement disorders.

Possible relation of atypical parkinsonism in the French West Indies with consumption of tropical plants: a case-control study. Caribbean Parkinsonism Study Group.

Coenzyme Q10 administration and its potential for treatment of neurodegenerative diseases.

Management of psychotic aspects of Parkinson's disease.

[Diagnosis and therapy of constipation]

Effects of pramipexole on contraversive rotation and functional motor impairments in 1-methyl-4-phenyl1,2,3, 6-tetrahydropyridine-induced chronic hemiparkinsonian monkeys.

Effects of talipexole on contraversive rotation and functional impairment in MPTP-induced chronic hemiparkinsonian monkeys.

Safety of selegiline (deprenyl) in the treatment of Parkinson's disease.

Non-drug therapies are highly beneficial in Parkinson's disease, but seldom prescribed.

Experience with tranylcypromine in early Parkinson's disease.

Medical treatment of essential tremor and Parkinson's disease.

Postprandial hypotension and parkinsonian state in Parkinson's disease.

Single case evaluation of the effects of aromatherapy and massage on disturbed behaviour in severe dementia.

The need for levodopa as an end point of Parkinson's disease progression in a clinical trial of selegiline and alpha-tocopherol. Parkinson Study Group.

Creatine supplementation in Parkinson disease: a placebo-controlled randomized pilot trial.

[A transcultural view of neurological and mental pathology in a Tzeltal Maya community of the Altos Chiapas]

Accidental choke-cherry poisoning: early symptoms and neurological sequelae of an unusual case of cyanide intoxication.

Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study.

Dysphagia and dementia in subjects with Parkinson's disease.

Selegiline in the treatment of narcolepsy.

Reproductive and developmental toxicity of the dopamine agonist pergolide mesylate in mice.

Dementia, depression, and nutritional status.

Preclinical toxicology studies with the new dopamine agonist pergolide. Acute, subchronic, and chronic evaluations.

A study of the nutritional status of elderly patients with Parkinson's disease.

GI motility disorders: diagnostic workup and use of prokinetic therapy.

Mitochondrial DNA variants observed in Alzheimer disease and Parkinson disease patients.

Is atypical parkinsonism in the Caribbean caused by the consumption of Annonaceae?

Facilitating self-care in clients with Parkinson's disease.

Parkinsonism treatment: Part III--Update.

Clinical and demographic data in 75 patients with near-fatal choking episodes.

[Irreversible neurologic sequelae caused by lithium]

A model for multisystem evaluation, interpretation, and treatment of individuals with neurologic dysfunction.

[Neurologic complications of drug addiction. General aspects.  
Complications caused by cannabis, designer drugs and volatile substances]

A natural and broad spectrum nootropic substance for treatment of SDAT--the Ginkgo biloba extract.

[Various aspects of Parkinson syndrome in the aged]

Levels of gamma-aminobutyric acid in cerebrospinal fluid in various neurologic disorders.

Weight changes with depot neuroleptic maintenance therapy.

Drugs, alcohol and driving.

[Hyperuricemia due to therapeutic measures]

Disposition of catecholamine-derived alkaloids in mammalian systems.

Intestinal malabsorption in the elderly.

Are neurodegenerative disorder and psychotic manifestations avoidable brain dysfunctions with adequate dietary omega-3?

Efficacy and safety of herbal medicines for idiopathic Parkinson's disease: a systematic review.

A semantically enabled formalism for the knowledge management of Parkinson's disease.

Dose ranging and efficacy study of high-dose coenzyme Q10 formulations in Huntington's disease mice.

Food habits and intake of nutrients in elderly patients with Parkinson's disease.

Use of nutritional supplements in Parkinson's disease patients.

Nutritional therapies in Parkinson's disease.

Initial treatment of Parkinson's disease.

Gluten sensitivity in Japanese patients with adult-onset cerebellar ataxia.

Comparison of region-of-interest analysis and human observers in the diagnosis of Parkinson's disease using [<sup>99m</sup>Tc]TRODAT-1 and SPECT.

Recent advances in Parkinson's disease therapy: use of monoamine oxidase inhibitors.

Extrapyramidal parkinsonism complicating acute organophosphate insecticide poisoning.

Nursing time to program and assess deep brain stimulators in movement disorder patients.

Manganese-induced Parkinsonism in a patient undergoing maintenance hemodialysis.

Atypical unclassifiable parkinsonism on Guadeloupe: an environmental toxic hypothesis.

[Systematic evaluation on clinical literature related with treatment of Parkinson's disease with traditional Chinese medicine]

Quantification of acetogenins in *Annona muricata* linked to atypical parkinsonism in guadeloupe.

Endothelial function markers in parkinsonian patients with hyperhomocysteinemia.

Predictors of freezing in Parkinson's disease: a survey of 6,620 patients.

Is complementary and alternative medicine (CAM) cost-effective? A systematic review.

Herb-drug interactions: a literature review.

Teaching people with Parkinson's disease about their medication.

Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study.

Enhanced biofilm-production in pathogens isolated from patients with rare metabolic disorders.

Beans, roots and leaves: a brief history of the pharmacological therapy of parkinsonism.

Chronic Intestinal Pseudo-Obstruction.

Taste responses in patients with Parkinson's disease.

Antiparkinsonian-like effects of *Plumbago scandens* on tremorine-induced tremors methodology.

Life style risks of Parkinson's disease: association between decreased water intake and constipation.

Management of acid-related disorders in patients with dysphagia.

Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study.

Cannabis sativa and dystonia secondary to Wilson's disease.

Dyskinesias due to intravenous apomorphine abuse in a patient without basal ganglia disorder.

Systematic assessment of decision models in Parkinson's disease.

Quercetin, a bioflavonoid, reverses haloperidol-induced catalepsy.

Resistance training with creatine monohydrate improves upper-body strength in patients with Parkinson disease: a randomized trial.

Atypical parkinsonism in Guadeloupe: a common risk factor for two closely related phenotypes?

Detection and determination of reticuline and N-methylcoculaurine in the Annonaceae family using liquid chromatography-tandem mass spectrometry.

Selegiline transdermal system: in the treatment of major depressive disorder.

Pharmacokinetics and pharmacodynamics of safinamide, a neuroprotectant with antiparkinsonian and anticonvulsant activity.

Parkinson's disease, palliative care and older people: Part 1.

Dopamine transporter binding study in differentiating carbon disulfide induced parkinsonism from idiopathic parkinsonism.

[Clinical observation on the efficacy enhancing and toxicity attenuating effect of nuzhen yangyin granule to the anti-parkinsonism therapy mainly with Medopa]

Dopamine transporter imaging and SPECT in diagnostic work-up of Parkinson's disease: a decision-analytic approach.

High doses of riboflavin and the elimination of dietary red meat promote the recovery of some motor functions in Parkinson's disease patients.

[Clinical manifestations of urinary disorders and their treatment in ageing men]

Diagnostic criteria for Parkinson's disease.

Weight loss in Parkinson's disease.

Gait and Balance Dysfunction in Adults.

Are neurodegenerative disorder and psychotic manifestations avoidable brain dysfunctions with adequate dietary omega-3?

[Nutritional study in geriatric patients (older than 65 years of age) with ambulatory enteral nutrition: correlation between underlying disease, nutritional support, and drug treatment]

Parkinson's disease: implications for nutritional care.

General geriatrics and gastroenterology: constipation and faecal incontinence.

Functional (Nonulcer) Dyspepsia.

Life-threatening parkinsonism induced by kava-kava.

### **Cluster 3 – Risk Factors**

intak 9.7%, risk 8.1%, smoke 5.6%, mao 4.7%, vitamin 3.3%, food 2.6%, women 1.8%, dietari 1.7%, men 1.7%, exposur 1.6%, tobacco 1.5%, fat 1.4%, mortal 1.2%, incid 1.2%, control 1.1%, trend 1.0%, case 1.0%, cohort 1.0%, tiq 0.9%, ag 0.9%

[Exposure to electromagnetic fields and risk of central nervous system diseases among employees at Danish electric companies]

Does a vegan diet reduce risk for Parkinson's disease?

Time trends in the incidence of parkinsonism in Olmsted County, Minnesota.

Frequency of bowel movements and the future risk of Parkinson's disease.

Neuroprotection in the MPTP Parkinsonian C57BL/6 mouse model by a compound isolated from tobacco.

Assessment of energy requirements in elderly populations.

Exposure to electromagnetic fields and risk of central nervous system disease in utility workers.

Association of coffee and caffeine intake with the risk of Parkinson disease.

Adult nutrient intake as a risk factor for Parkinson's disease.

MAO-A and -B gene knock-out mice exhibit distinctly different behavior.

[Do antioxidants in the diet affect the risk of developing Parkinson disease?]

Epidemiologic approaches to the study of Parkinson's disease etiology.

Monoamine oxidase: from genes to behavior.

Dietary factors in Parkinson's disease: the role of food groups and specific foods.



Studies on the interaction between 1,2,3,4-tetrahydro-beta-carboline and cigarette smoke: a potential mechanism of neuroprotection for Parkinson's disease.

Dietary iron, animal fats, and risk of Parkinson's disease.

A case-referent study of extrapyramidal signs (preparkinsonism) in rural communities of Israel.

Increased stress response and beta-phenylethylamine in MAOB-deficient mice.

Dietary antioxidants and Parkinson disease. The Rotterdam Study.

Employment as a welder and Parkinson disease among heavy equipment manufacturing workers.

The epidemiology of Parkinson's disease.

Dietary antioxidants and other dietary factors in the etiology of Parkinson's disease.

Inhibition of brain monoamine oxidase by adducts of 1,2,3,4-tetrahydroisoquinoline with components of cigarette smoke.

Diet and Parkinson's disease. II: A possible role for the past intake of specific nutrients. Results from a self-administered food-frequency questionnaire in a case-control study.

Diet and Parkinson's disease. I: A possible role for the past intake of specific foods and food groups. Results from a self-administered food-frequency questionnaire in a case-control study.

Two case reports of neurological disease in coal mine preparation plant workers.

Interaction of 1,2,3,4-tetrahydroisoquinoline with some components of cigarette smoke: potential implications for Parkinson's Disease.

Epidemiology of Parkinson's disease.

Case-control study of idiopathic Parkinson's disease and dietary vitamin E intake.

Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study.

Food, dietetics and nutrition in ancient India.

A case-control study of Parkinson's disease in a horticultural region of British Columbia.

[A case-control study of Parkinson's disease]

Environmental antecedents of young-onset Parkinson's disease.

A case-control study on the environmental risk factors of Parkinson's disease in Tianjin, China.

Induction of cytochrome P-450 enzymes via tobacco smoke: a potential mechanism for developing resistance to environmental toxins as related to parkinsonism and other neurologic diseases.

Diet, body size and micronutrient status in Parkinson's disease.

Cytochrome P450 isozymes catalyzing 4-hydroxylation of parkinsonism-related compound 1,2,3,4-tetrahydroisoquinoline in rat liver microsomes.

[Parkinson's disease and environmental factors]

Parkinson's disease: a case-control study of occupational and environmental risk factors.

Follow-up study of early-life protective and risk factors in Parkinson's disease.

Epidemiologic study of Parkinson's disease in Hong Kong.

Environmental factors and Parkinson's disease: a case-control study in China.

Fenuafala health survey: the ecology of health and disease on a coral atoll village.

Epidemiologic study on the association between body burden mercury level and idiopathic Parkinson's disease.

Case-control study of early life dietary factors in Parkinson's disease.

Extrapyramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure.

Presence of tetrahydroisoquinoline and 1-methyl-tetrahydro-isoquinoline in foods: compounds related to Parkinson's disease.

Irreversible inhibition of monoamine oxidase by some components of cigarette smoke.

Cigarette smoking and Parkinson's disease.

Synergistic neurotoxicity of carbon tetrachloride/carbon disulfide (80/20 fumigants) and other pesticides in grain storage workers.

Dietary folate, vitamin B12, and vitamin B6 and the risk of Parkinson disease.

Motor alterations associated with exposure to manganese in the environment in Mexico.

Update: cohort mortality study of workers highly exposed to polychlorinated biphenyls (PCBs) during the manufacture of electrical capacitors, 1940-1998.

Dietary factors and smoking as risk factors for PD in a rural population in China: a nested case-control study.

Isolation and characterization of a monoamine oxidase B selective inhibitor from tobacco smoke.

Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohort.

Older women and dietary advice: occurrence, comprehension and compliance.

Nutritional aspects of manganese homeostasis.

Smokeless tobacco use and the risk of Parkinson's disease mortality.

Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study.

Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis.

Monoamine oxidase B (MAO-B) inhibition by active principles from *Uncaria rhynchophylla*.

Promoting effect and recovery activity from physical stress of the fruit of *Morus alba*.

Five-day food intake in elderly female outpatients with Parkinson's disease, rheumatoid arthritis or stroke.

Folate intake and risk of Parkinson's disease.

Exposure to beta-carbolines norharman and harman.

Consumption of dairy products and risk of Parkinson's disease.

[Exposure to neurotoxic metals and prevalence of parkinsonian syndrome in the area of Brescia]

Tobacco leaf, smoke and smoking, MAO inhibitors, Parkinson's disease and neuroprotection; are there links?

Cloning, after cloning, knock-out mice, and physiological functions of MAO A and B.

Retrospective study of preventive effect of maize on mortality from Parkinson's disease in Japan.

Environmental, life-style, and physical precursors of clinical Parkinson's disease: recent findings from the Honolulu-Asia Aging Study.

Meals and snacks among elderly self-managing and disabled women.

Activities of extract and constituents of *Banisteriopsis caapi* relevant to parkinsonism.

Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes.

Dietary intakes of fat and risk of Parkinson's disease.

Vitamin D and Parkinson's disease--a hypothesis.

[Parkinson s disease risk factors]

[Parkinson's disease, tobacco and age: meta analysis]

Lifestyle, health and disease prevention: the underlying mechanisms.

Manganese: pharmacokinetics and molecular mechanisms of brain uptake.

Diet and Parkinson's disease: a potential role of dairy products in men.

Intakes of vitamins E and C, carotenoids, vitamin supplements, and PD risk.

Mortality among a cohort of banana plantation workers in Costa Rica.

Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake.

#### **Cluster 4 – Factors in Aging-Related Neurodegenerative Diseases**

ag 2.8%, antioxid 2.1%, diet 1.6%, radic 1.5%, dietari 1.5%, vitamin 1.4%, brain 1.4%, disord 1.3%, oxid 1.3%, supplement 1.2%, alzheimer 1.2%, plant 1.1%, free 1.0%, compound 0.9%, stress 0.8%, creatin 0.8%, health 0.8%, damag 0.7%, cancer 0.7%, metabol 0.7%

Hagfish in the New Zealand fjords are supported by chemoautotrophy of forest carbon.

Genetically engineered mice and their use in aging research.

Mitochondrial dysfunction, free radical generation and cellular stress response in neurodegenerative disorders.

Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment.

Ketone bodies, potential therapeutic uses.

[Oxidative stress and human disease. Current knowledge and perspectives for prevention]

[Neurological anthropology among the Kamayura Indians of the Alto Xingu]

Clinical pharmacology of the dietary supplement creatine monohydrate.

A possible emerging role of phytochemicals in improving age-related neurological dysfunctions: a multiplicity of effects.

Variations in dietary iron alter behavior in developing rats.

Beneficial effect(s) of n-3 fatty acids in cardiovascular diseases: but, why and how?

Neuroprotective signaling and the aging brain: take away my food and let me run.

Nutraceutical interventions may delay aging and the age-related diseases.

Potential benefits of creatine monohydrate supplementation in the elderly.

Relationships among diet, physical activity and other lifestyle factors and debilitating diseases in the elderly.

Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention.

Diet and apoptosis.

Essential fatty acids and the brain: possible health implications.

Iron deficient and manganese supplemented diets alter metals and transporters in the developing rat brain.

Monograph series on aging-related diseases: XII. Parkinson's disease--recent developments and new directions.

Studies on the pyrrolinone metabolites derived from the tobacco alkaloid 1-methyl-2-(3-pyridinyl)pyrrole (beta-nicotyrine).

Multiple system atrophy.

Polymorphic cytochromes P450 and drugs used in psychiatry.

Acute stressor-selective effects on homocysteine metabolism and oxidative stress parameters in female rats.

Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults.

[Xenografts: clinical trials and perspectives]

Free radical scavenging activity of fermented papaya preparation and its effect on lipid peroxide level and superoxide dismutase activity in iron-induced epileptic foci of rats.

Antioxidant vitamins in prevention.

Cellular and molecular neurosurgery: pathways from concept to reality--part I: target disorders and concept approaches to gene therapy of the central nervous system.

Phenotypic variation in xenobiotic metabolism and adverse environmental response: focus on sulfur-dependent detoxification pathways.

Variables associated with cognitive function in elderly California Seventh-day Adventists.

Vitamin E in humans: demand and delivery.

Recent studies on the zoopharmacognosy, pharmacology and neurotoxicology of sesquiterpene lactones.

Oxidative stress: the paradox of aerobic life.

Parkinson's disease: a chronic, low-grade antioxidant deficiency?

Free radicals, antioxidants and preventive geriatrics.

[Jean-Martin Charcot, his time and Kinnosuke Miura]

L-tryptophan in neuropsychiatric disorders: a review.

Transformations of (+-)-salsolinol into optically active O- and/or N-methylated derivatives by several Papaveraceae plants and their tissue-cultured cells.

Low copper status of rats affects polyunsaturated fatty acid composition of brain phospholipids, unrelated to neuropathology.

Cellular clones and transgenic mice overexpressing copper-zinc superoxide dismutase: models for the study of free radical metabolism and aging.

Magnesium inhibits the harmful effects on plants of some toxic elements.

Bioassay-guided isolation of antiatherosclerotic phytochemicals from *Artocarpus altilis*.



Inhibiting noradrenergic overactivity by inhibition of thromboxane and concomitant activation of opiate receptors via dietary means.

Tomatoes and Parkinson's disease.

Disease family trees: the possible roles of iodine in goitre, cretinism, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's and Parkinson's diseases and cancers of the thyroid, nervous system and skin.

Dietary precursors and brain neurotransmitter formation.

Neuroprotective and disease-modifying effects of the ketogenic diet.

Dietary chelators as antioxidant enzyme mimetics: implications for dietary intervention in neurodegenerative diseases.

Caloric restriction and intermittent fasting: two potential diets for successful brain aging.

Working memory deficits in transgenic rats overexpressing human adenosine A2A receptors in the brain.

Fruit polyphenols and their effects on neuronal signaling and behavior in senescence.

[Effect of vitamin D on the nervous system and the skeletal muscle]

A manganese-enhanced diet alters brain metals and transporters in the developing rat.

Antioxidants, supplements, and Parkinson's disease.

High-resolution large-scale mosaic imaging using multiphoton microscopy to characterize transgenic mouse models of human neurological disorders.

The effect on health of alternate day calorie restriction: eating less and more than needed on alternate days prolongs life.

Use of ginseng in medicine with emphasis on neurodegenerative disorders.

Synthesis of novel benzofuran isoxazolines as protein tyrosine phosphatase 1B inhibitors.

Green tea and its polyphenolic catechins: medicinal uses in cancer and noncancer applications.

Nutritional intervention in brain aging: reducing the effects of inflammation and oxidative stress.

Herbal complement inhibitors in the treatment of neuroinflammation: future strategy for neuroprotection.

Neurodegeneration from mitochondrial insufficiency: nutrients, stem cells, growth factors, and prospects for brain rebuilding using integrative management.

Nicotinamide: a double edged sword.

Antioxidant properties and PC12 cell protective effects of APS-1, a polysaccharide from *Aloe vera* var. *chinensis*.

[Vegetarian diets; effect on health]

Proceedings from the "Third International Conference on Mechanism of Action of Nutraceuticals".

HPLC determination of free nitrogenous compounds of *Centaurea solstitialis* (Asteraceae), the cause of equine nigropallidal encephalomalacia.

International conference on the healthy effect of virgin olive oil.

Unique properties of polyphenol stilbenes in the brain: more than direct antioxidant actions; gene/protein regulatory activity.

Natural products and derivatives affecting neurotransmission relevant to Alzheimer's and Parkinson's disease.

Brain, aging and neurodegeneration: role of zinc ion availability.

Nicotinamide homeostasis: a xenobiotic pathway that is key to development and degenerative diseases.

Evaluation of hepatoprotective potential of HESA-A (a marine compound) pretreatment against thioacetamide-induced hepatic damage in rabbits.

Cognitive decline, neuromotor and behavioural disturbances in a mouse model for fragile-X-associated tremor/ataxia syndrome (FXTAS).

Application of nicotine enantiomers, derivatives and analogues in therapy of neurodegenerative disorders.

Prophylactic activation of neuroprotective stress response pathways by dietary and behavioral manipulations.

Neuroprotection from complement-mediated inflammatory damage.

Glucose, glycation and aging.

Why do we need new gene therapy viral vectors? Characteristics, limitations and future perspectives of viral vector transduction.

*Salviae miltiorrhizae* radix inhibits superoxide generation by activated rat microglia and mimics the action of amphetamine on in vitro rat striatal dopamine release.

Peroxynitrite scavenging mode of alaternin isolated from *Cassia tora*.

A possible cause and corresponding treatment for inflammatory, auto-immune or auto-aggressive diseases.

Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases.

Neurotoxicant-induced animal models of Parkinson's disease: understanding the role of rotenone, maneb and paraquat in neurodegeneration.

[Cannabis and cannabinoid receptors: from pathophysiology to therapeutic options]

Metals in our minds: therapeutic implications for neurodegenerative disorders.

Transgenic nonhuman primates for neurodegenerative diseases.

Approach to the problems of the aged.

Redox regulation of cellular stress response in neurodegenerative disorders.

Cell signaling pathways in the neuroprotective actions of the green tea polyphenol (-)-epigallocatechin-3-gallate: implications for neurodegenerative diseases.

CNS dopamine oxidation and catechol-O-methyltransferase: importance in the etiology, pharmacotherapy, and dietary prevention of Parkinson's disease.

The many roles of apoptosis in immunity as modified by aging and nutritional status.

Inhibition of peroxynitrite-mediated reactions by vanillin.

Neuroprotection by bioactive components in medicinal and food plant extracts.

"Brain-specific" nutrients: a memory cure?

Ketones: metabolism's ugly duckling.

[Therapeutic use of cannabinoids in neurology]

Gene-diet interactions in brain aging and neurodegenerative disorders.

Tissue histopathology, clinical chemistry and behaviour of adult Comt-gene-disrupted mice.

Vitamin E therapy in Parkinson's disease.

Iron interactions and other biological reactions mediating the physiological and toxic actions of manganese.

Ketoacids? Good medicine?

Methylation and acetylation in nervous system development and neurodegenerative disorders.

[Neurological syndromes linked with the intake of plants and fungi containing a toxic component (I). Neurotoxic syndromes caused by the ingestion of plants, seeds and fruits]

Mitochondrial avid radioprobes. Preparation and evaluation of 7'(Z)-[125I]iodorotenone and 7'(Z)-[125I]iodorotenol.

Bioenergetic approaches for neuroprotection in Parkinson's disease.

Screening of antioxidant activity of three Indian medicinal plants, traditionally used for the management of neurodegenerative diseases.

Methodological considerations for characterizing potential antioxidant actions of bioactive components in plant foods.

Will caloric restriction and folate protect against AD and PD?

Meal size and frequency affect neuronal plasticity and vulnerability to disease: cellular and molecular mechanisms.

Selenium intake, mood and other aspects of psychological functioning.

Redox regulation of cellular stress response in aging and neurodegenerative disorders: role of vitagenes.

Roles of vitamins E and C on neurodegenerative diseases and cognitive performance.

Role of oxidative stress and antioxidants in neurodegenerative diseases.

Alkaloids, alcohol and Parkinson's disease.

[Antioxidants to slow aging, facts and perspectives]

Catechol-O-Methyltransferase (COMT)-mediated methylation metabolism of endogenous bioactive catechols and modulation by endobiotics and xenobiotics: importance in pathophysiology and pathogenesis.

Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease?

Tetrahydrobiopterin biosynthesis, utilization and pharmacological effects.

Chemical and physical properties and potential mechanisms: melatonin as a broad spectrum antioxidant and free radical scavenger.

Guidelines for brain radionuclide imaging. Perfusion single photon computed tomography (SPECT) using Tc-99m radiopharmaceuticals and brain metabolism positron emission tomography (PET) using F-18 fluorodeoxyglucose. The Belgian Society for Nuclear Medicine.

## **Cluster 5 – Neurotoxic Factors for Parkinson’s and Amyotrophic Lateral Sclerosis, emphasizing Plants/Seeds**

cycad 8.4%, al 6.8%, bmaa 4.6%, amyotroph 2.9%, amyotrophic.lateral.sclerosis 2.9%, amyotrophic.lateral 2.9%, lateral.sclerosis 2.9%, later 2.7%, sclerosi 2.7%, guam 1.6%, neurodegen 1.3%, pdc 1.2%, seed 1.1%, chamorro 0.9%, fly 0.8%, flour 0.8%, disord 0.8%, als.pdc 0.7%, parkinsonism.dementia 0.7%, neurofila 0.6%

Mice, the motor system, and human motor neuron pathology.

Nitric oxide synthases: targets for therapeutic strategies in neurological diseases.

[Recent progress in the research field on triplet repeat diseases]

Cycad exposure and risk of dementia, MCI, and PDC in the Chamorro population of Guam.

Did consumption of flour bleached by the agene process contribute to the incidence of neurological disease?

The Guam cycad toxin methylazoxymethanol damages neuronal DNA and modulates tau mRNA expression and excitotoxicity.

Genetic neurodegenerative diseases: the human illness and transgenic models.

Neurofilaments in health and disease.

Metabolic dysfunction in familial, but not sporadic, amyotrophic lateral sclerosis.

Electrical occupations and neurodegenerative disease: analysis of U.S. mortality data.

Use of genetically engineered mice as models for exploring the role of oxidative stress in neurodegenerative diseases.

A novel neurological phenotype in mice lacking mitochondrial manganese superoxide dismutase.

[Disappearance of ALS from Guam: implications for exogenous causes]

Screening for non-protein amino acids in seeds of the Guam cycad, *Cycas circinalis*, by an improved GC-MS method.

Apoptosis in brain and gut tissue of mice fed a seed preparation of the cycad *Lepidozamia peroffskyana*.

Billion-fold difference in the toxic potencies of two excitatory plant amino acids, L-BOAA and L-BMAA: biochemical and morphological studies using mouse brain slices.

Fasting plasma and CSF amino acid levels in amyotrophic lateral sclerosis: a subtype analysis.

Neurologic diseases associated with use of plant components with toxic potential.

Probing modifications of the neuronal cytoskeleton.

New insights on the pathogenesis of neurodegenerative disorders.

Content of the neurotoxins cycasin (methylazoxymethanol beta-D-glucoside) and BMAA (beta-N-methylamino-L-alanine) in cycad flour prepared by Guam Chamorros.

Facilitated transport of the neurotoxin, beta-N-methylamino-L-alanine, across the blood-brain barrier.

Long-latency neurodegenerative disease in the western Pacific.

Slow toxins, biologic markers, and long-latency neurodegenerative disease in the western Pacific region.

2-Amino-3-(methylamino)-propanoic acid (BMAA) in cycad flour: an unlikely cause of amyotrophic lateral sclerosis and parkinsonism-dementia of Guam.

Low-calcium, high-aluminum diet-induced motor neuron pathology in cynomolgus monkeys.



Determination of beta-N-methylamino-L-alanine (BMAA) in plant (*Cycas circinalis* L.) and animal tissue by precolumn derivatization with 9-fluorenylmethyl chloroformate (Fmoc) and reversed-phase high-performance liquid chromatography.

Histochemical and X-ray microanalytical localization of aluminum in amyotrophic lateral sclerosis and parkinsonism-dementia of Guam.

Observations about amyotrophic lateral sclerosis and the parkinsonism-dementia complex of Guam with regard to epidemiology and etiology.

Guam ALS/parkinsonism-dementia: a long-latency neurotoxic disorder caused by "slow toxin(s)" in food?

Guam amyotrophic lateral sclerosis-parkinsonism-dementia linked to a plant excitant neurotoxin.

Amyotrophic lateral sclerosis and parkinsonian syndromes in high incidence among the Auyu and Jakai people of West New Guinea.

Mitochondrial DNA polymerase-gamma and human disease.

Geographic isolates of atypical Parkinsonism and tauopathy in the tropics: possible synergy of neurotoxins.

Mitochondrial DNA mutations and aging.

BMAA selectively injures motor neurons via AMPA/kainate receptor activation.

Magnesium deficiency over generations in rats with special references to the pathogenesis of the Parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam.

*Drosophila* models pioneer a new approach to drug discovery for Parkinson's disease.

Genetics of familial and sporadic amyotrophic lateral sclerosis.

Inhibition of amyloid fibril formation by polyphenols: structural similarity and aromatic interactions as a common inhibition mechanism.

Cycad toxins, *Helicobacter pylori* and parkinsonism: cholesterol glucosides as the common denominator.

[RNAi and neurological disease]

Prion 2005: Between Fundamentals and Society's Needs.

The effect of epigallocatechin gallate on suppressing disease progression of ALS model mice.

*Drosophila* as a model for human neurodegenerative disease.

The beneficial effects of fruit polyphenols on brain aging.

On the decline and etiology of high-incidence motor system disease in West Papua (southwest New Guinea).

Return of the cycad hypothesis - does the amyotrophic lateral sclerosis/parkinsonism dementia complex (ALS/PDC) of Guam have new implications for global health?

Nature, nurture and neurology: gene-environment interactions in neurodegenerative disease. FEBS Anniversary Prize Lecture delivered on 27 June 2004 at the 29th FEBS Congress in Warsaw.

Examining the interaction of apo E and neurotoxicity on a murine model of ALS-PDC.

Neurodegenerative conditions associated with ageing: a molecular interplay?

A behavioural characterisation of the FVB/N mouse strain.

Quantitative measurement of neurodegeneration in an ALS-PDC model using MR microscopy.

A mechanism for slow release of biomagnified cyanobacterial neurotoxins and neurodegenerative disease in Guam.

Transglutaminases - possible drug targets in human diseases.

Identification and expression of the gene for human ataxin-2-related protein on chromosome 16.

A rapid cellular FRET assay of polyglutamine aggregation identifies a novel inhibitor.

Biomagnification of cyanobacterial neurotoxins and neurodegenerative disease among the Chamorro people of Guam.

Analysis of neurological disease in four dimensions: insight from ALS-PDC epidemiology and animal models.

Calcium-dependent and aspartyl proteases in neurodegeneration and ageing in *C. elegans*.

Parkinson's disease mice and human umbilical cord blood.

Biomagnification of cycad neurotoxins in flying foxes: implications for ALS-PDC in Guam.

From fruit fly to bedside: translating lessons from *Drosophila* models of neurodegenerative disease.

Stem therapy for ALS: hope and reality.

In vivo NMR studies of neurodegenerative diseases in transgenic and rodent models.

Neurofilaments and neurological disease.

Dying for a cause: invertebrate genetics takes on human neurodegeneration.

The fly as a model for neurodegenerative diseases: is it worth the jump?

Nutritional issues and supplements in amyotrophic lateral sclerosis and other neurodegenerative disorders.

A review of specific dietary antioxidants and the effects on biochemical mechanisms related to neurodegenerative processes.

Role of superoxide dismutases in oxidative damage and neurodegenerative disorders.

Transgenic mouse models of neurodegenerative disease: opportunities for therapeutic development.

Animal models of PD: pieces of the same puzzle?

Isolation of various forms of sterol beta-D-glucoside from the seed of *Cycas circinalis*: neurotoxicity and implications for ALS-parkinsonism dementia complex.

Behavioral and neurological correlates of ALS-parkinsonism dementia complex in adult mice fed washed cycad flour.

Coenzyme Q10 as a possible treatment for neurodegenerative diseases.

Modelling neurodegenerative diseases in *Drosophila*: a fruitful approach?

Synergistic versus antagonistic actions of glutamate and glutathione: the role of excitotoxicity and oxidative stress in neuronal disease.

Novel environmental toxins: sterol glycosides as a potential etiological factor for age-related neurodegenerative diseases.

Cycad neurotoxins, consumption of flying foxes, and ALS-PDC disease in Guam.

Engineered modeling and the secrets of Parkinson's disease.

## LABORATORY RESEARCH STUDIES

### **Cluster 6 - Rotenone-induced Degeneration of Dopaminergic Neurons.**

rotenon 32.9%, complex 4.6%, mitochondri 2.7%, rotenone.induced 2.2%, rat 1.7%, induc 1.3%, inhibit 1.2%, cell 1.1%, dopaminerg 1.1%, inhibitor 1.0%, mpp 0.9%, toxic 0.8%, neuron 0.8%, atp 0.7%, activ 0.7%, apoptosi 0.7%, exposur 0.5%, dopamin 0.5%, oxid 0.5%, infus 0.5%

Distinct role for microglia in rotenone-induced degeneration of dopaminergic neurons.

Caspase-3 activation induced by inhibition of mitochondrial complex I is facilitated by glycogen synthase kinase-3beta and attenuated by lithium.

Neuroprotective effects of ginsenoside-Rg1 in primary nigral neurons against rotenone toxicity.

Selective dopaminergic vulnerability: 3,4-dihydroxyphenylacetaldehyde targets mitochondria.

Chronic reduction in complex I function alters calcium signaling in SH-SY5Y neuroblastoma cells.

Mitochondria deficient in complex I activity are depolarized by hydrogen peroxide in nerve terminals: relevance to Parkinson's disease.

Increased striatal dopamine turnover following acute administration of rotenone to mice.

In vivo labeling of mitochondrial complex I (NADH:ubiquinone oxidoreductase) in rat brain using [(3)H]dihydrorotenone.

The selective toxicity of 1-methyl-4-phenylpyridinium to dopaminergic neurons: the role of mitochondrial complex I and reactive oxygen species revisited.

3,4-Dihydroxyphenylacetaldehyde potentiates the toxic effects of metabolic stress in PC12 cells.

Metabolic stress in PC12 cells induces the formation of the endogenous dopaminergic neurotoxin, 3,4-dihydroxyphenylacetaldehyde.

Transglutaminase 2 ablation leads to defective function of mitochondrial respiratory complex I affecting neuronal vulnerability in experimental models of extrapyramidal disorders.

Impaired glutamate clearance as a consequence of energy failure caused by MPP(+) in astrocytic cultures.

Depolarization of in situ mitochondria due to hydrogen peroxide-induced oxidative stress in nerve terminals: inhibition of alpha-ketoglutarate dehydrogenase.

Carnosol, a component of rosemary (*Rosmarinus officinalis* L.) protects nigral dopaminergic neuronal cells.

Interaction of alpha-phenyl-N-tert-butyl nitron and alternative electron acceptors with complex I indicates a substrate reduction site upstream from the rotenone binding site.

Cyclosporin inhibition of apoptosis induced by mitochondrial complex I toxins.

Obligatory role for complex I inhibition in the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

Quantitative study of mitochondrial complex I in platelets of parkinsonian patients.

Metabolic inhibition enhances selective toxicity of L-DOPA toward mesencephalic dopamine neurons in vitro.

Free radical scavengers protect dopaminergic cell lines from apoptosis induced by complex I inhibitors.

The content of intracellular mitochondrial DNA is decreased by 1-methyl-4-phenylpyridinium ion (MPP+).

Systemic administration of rotenone produces selective damage in the striatum and globus pallidus, but not in the substantia nigra.

[3H]dihydrorotenone binding to NADH: ubiquinone reductase (complex I) of the electron transport chain: an autoradiographic study.

Differential effect of nerve growth factor on dopaminergic neurotoxin-induced apoptosis.

Assay of [3H]dihydrorotenone binding to complex I in intact human platelets.

Synthesis and biological evaluation in mice of (2-[11C]methoxy)-6',7'-dihydrorotenol, a second generation rotenoid for marking mitochondrial complex I activity.

Synthesis of (2-[11C]methoxy)rotenone, a marker of mitochondrial complex I activity.

Divergent mechanisms of paraquat, MPP<sup>+</sup>, and rotenone toxicity: oxidation of thioredoxin and caspase-3 activation.

Controversies on new animal models of Parkinson's disease pro and con: the rotenone model of Parkinson's disease (PD).

The rotenone model of parkinsonism--the five years inspection.

Quantitative autoradiography of dihydrorotenone binding to complex I of the electron transport chain.

Therapy of Morbus Parkinson and radical-induced neurotoxicity in the rat--in vivo voltammetric studies.

Interaction of 1-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>) and its analogs with the rotenone/piericidin binding site of NADH dehydrogenase.

D-beta-hydroxybutyrate protects dopaminergic SH-SY5Y cells in a rotenone model of Parkinson's disease.

Neurotrophic factors stabilize microtubules and protect against rotenone toxicity on dopaminergic neurons.

Proteasome inhibition and Parkinson's disease modeling.

Rats with unilateral median forebrain bundle, but not striatal or nigral, lesions by the neurotoxins MPP<sup>+</sup> or rotenone display differential sensitivity to amphetamine and apomorphine.

Monocyte-mediated rotenone neurotoxicity towards human neuroblastoma SH-SY5Y: role of mitogen-activated protein kinases.

Complex-1 activity and 18F-DOPA uptake in genetically engineered mouse model of Parkinson's disease and the neuroprotective role of coenzyme Q10.

Neurodegeneration of mouse nigrostriatal dopaminergic system induced by repeated oral administration of rotenone is prevented by 4-phenylbutyrate, a chemical chaperone.

Potentiating effect of the ATP-sensitive potassium channel blocker glibenclamide on complex I inhibitor neurotoxicity in vitro and in vivo.

Basic fibroblast growth factor protects against rotenone-induced dopaminergic cell death through activation of extracellular signal-regulated kinases 1/2 and phosphatidylinositol-3 kinase pathways.

Activation of group III metabotropic glutamate receptors attenuates rotenone toxicity on dopaminergic neurons through a microtubule-dependent mechanism.

Enhanced sensitivity of DJ-1-deficient dopaminergic neurons to energy metabolism impairment: role of Na<sup>+</sup>/K<sup>+</sup> ATPase.

Rotenone induces cell death in primary dopaminergic culture by increasing ROS production and inhibiting mitochondrial respiration.

Chromatographic analysis of dopamine metabolism in a Parkinsonian model.

Susceptibility to rotenone is increased in neurons from parkin null mice and is reduced by minocycline.



In vivo complementation of complex I by the yeast Ndi1 enzyme. Possible application for treatment of Parkinson disease.

L-deprenyl protects against rotenone-induced, oxidative stress-mediated dopaminergic neurodegeneration in rats.

Enhanced sensitivity of dopaminergic neurons to rotenone-induced toxicity with aging.

Behavioural and neural deficits induced by rotenone in the pond snail *Lymnaea stagnalis*. A possible model for Parkinson's disease in an invertebrate.

Rotenone and MPP<sup>+</sup> preferentially redistribute apoptosis-inducing factor in apoptotic dopamine neurons.

Early induction of calpains in rotenone-mediated neuronal apoptosis.

Tetrahydrobiopterin causes mitochondrial dysfunction in dopaminergic cells: implications for Parkinson's disease.

Valproic acid-mediated Hsp70 induction and anti-apoptotic neuroprotection in SH-SY5Y cells.

The regulation of rotenone-induced inflammatory factor production by ATP-sensitive potassium channel expressed in BV-2 cells.

Partial mitochondrial inhibition causes striatal dopamine release suppression and medium spiny neuron depolarization via H<sub>2</sub>O<sub>2</sub> elevation, not ATP depletion.

Rotenone model of Parkinson disease: multiple brain mitochondria dysfunctions after short term systemic rotenone intoxication.

Paraquat neurotoxicity is distinct from that of MPTP and rotenone.

A delivery strategy for rotenone microspheres in an animal model of Parkinson's disease.

Rotenone and CCCP inhibit tyrosine hydroxylation in rat striatal tissue slices.

Protective effect of melatonin on rotenone plus  $\text{Ca}^{2+}$ -induced mitochondrial oxidative stress and PC12 cell death.

Selective vulnerability of dopaminergic neurons to microtubule depolymerization.

Spare respiratory capacity rather than oxidative stress regulates glutamate excitotoxicity after partial respiratory inhibition of mitochondrial complex I with rotenone.

PACAP protects neuronal differentiated PC12 cells against the neurotoxicity induced by a mitochondrial complex I inhibitor, rotenone.

Dopaminergic neurotoxins require excitotoxic stimulation in organotypic cultures.

Behavioral differences in a rotenone-induced hemiparkinsonian rat model developed following intranigral or median forebrain bundle infusion.

Acute intranigral infusion of rotenone in rats causes progressive biochemical lesions in the striatum similar to Parkinson's disease.

Mitochondrial membrane depolarization and the selective death of dopaminergic neurons by rotenone: protective effect of coenzyme Q10.

Activation of mitochondrial ATP-sensitive potassium channels improves rotenone-related motor and neurochemical alterations in rats.

Increased sensitivity of striatal dopamine release to  $\text{H}_2\text{O}_2$  upon chronic rotenone treatment.

Angiotensin II protects cultured midbrain dopaminergic neurons against rotenone-induced cell death.

Energy status, ubiquitin proteasomal function, and oxidative stress during chronic and acute complex I inhibition with rotenone in mesencephalic cultures.

The effect of endogenous dopamine in rotenone-induced toxicity in PC12 cells.

Increased myocardial N-myristoyltransferase activity in rotenone model of Parkinsonism.

Sleep disturbances in the rotenone animal model of Parkinson disease.

Bioenergetics in glutaryl-coenzyme A dehydrogenase deficiency: a role for glutaryl-coenzyme A.

The parkinsonian neurotoxin rotenone activates calpain and caspase-3 leading to motoneuron degeneration in spinal cord of Lewis rats.

Systematic administration of iptakalim, an ATP-sensitive potassium channel opener, prevents rotenone-induced motor and neurochemical alterations in rats.

Rotenone induces oxidative stress and dopaminergic neuron damage in organotypic substantia nigra cultures.

Melatonin protects against rotenone-induced oxidative stress in a hemiparkinsonian rat model.

Possible involvement of  $\text{Ca}^{2+}$  signaling in rotenone-induced apoptosis in human neuroblastoma SH-SY5Y cells.

Neuroprotective effect of 1-methyl-1,2,3,4-tetrahydroisoquinoline on cultured rat mesencephalic neurons in the presence or absence of various neurotoxins.

Cytochrome c release from rat brain mitochondria is proportional to the mitochondrial functional deficit: implications for apoptosis and neurodegenerative disease.

Effect of sesamin in *Acanthopanax senticosus* HARMS on behavioral dysfunction in rotenone-induced parkinsonian rats.

Mitochondrial complex I inhibition depletes plasma testosterone in the rotenone model of Parkinson's disease.

Chronic exposure to rotenone models sporadic Parkinson's disease in *Drosophila melanogaster*.

Pramipexole protects against apoptotic cell death by non-dopaminergic mechanisms.

Rotenone, deguelin, their metabolites, and the rat model of Parkinson's disease.

Rotenone potentiates dopamine neuron loss in animals exposed to lipopolysaccharide prenatally.

Activation of c-Jun N-terminal protein kinase is a common mechanism underlying paraquat- and rotenone-induced dopaminergic cell apoptosis.

Distinct mechanisms of neurodegeneration induced by chronic complex I inhibition in dopaminergic and non-dopaminergic cells.

Sensitivity of zebrafish to environmental toxins implicated in Parkinson's disease.

Variable effects of chronic subcutaneous administration of rotenone on striatal histology.

Rotenone induces apoptosis via activation of bad in human dopaminergic SH-SY5Y cells.

L-DOPA reverses the hypokinetic behaviour and rigidity in rotenone-treated rats.

Effects of iptakalim on rotenone-induced cytotoxicity and dopamine release from PC12 cells.

Behavioral and immunohistochemical effects of chronic intravenous and subcutaneous infusions of varying doses of rotenone.

Neuroprotective effect of fraxetin and myricetin against rotenone-induced apoptosis in neuroblastoma cells.

The neurobehavioral changes induced by bilateral rotenone lesion in medial forebrain bundle of rats are reversed by L-DOPA.

Alpha-synuclein and tyrosine hydroxylase expression in acute rotenone toxicity.

Chronic administration of rotenone increases levels of nitric oxide and lipid peroxidation products in rat brain.

Rotenone-induced apoptosis is mediated by p38 and JNK MAP kinases in human dopaminergic SH-SY5Y cells.

Rotenone induces non-specific central nervous system and systemic toxicity.

Protective effect of 1-methyl-1,2,3,4-tetrahydroisoquinoline against dopaminergic neurodegeneration in the extrapyramidal structures produced by intracerebral injection of rotenone.

Annonacin, a lipophilic inhibitor of mitochondrial complex I, induces nigral and striatal neurodegeneration in rats: possible relevance for atypical parkinsonism in Guadeloupe.

Dopamine is involved in selectivity of dopaminergic neuronal death by rotenone.

Mechanism of toxicity in rotenone models of Parkinson's disease.

The pesticide rotenone induces caspase-3-mediated apoptosis in ventral mesencephalic dopaminergic neurons.

An inhibitor of mitochondrial complex I, rotenone, inactivates proteasome by oxidative modification and induces aggregation of oxidized proteins in SH-SY5Y cells.

Mechanism for generation of hydrogen peroxide and change of mitochondrial membrane potential during rotenone-induced apoptosis.

MPP<sup>+</sup> analogs acting on mitochondria and inducing neuro-degeneration.

The mitochondrial complex I inhibitor annonacin is toxic to mesencephalic dopaminergic neurons by impairment of energy metabolism.

Rotenone increases glutamate-induced dopamine release but does not affect hydroxyl-free radical formation in rat striatum.

Role of nitric oxide in rotenone-induced nigro-striatal injury.

Animal models of Parkinson's disease in rodents induced by toxins: an update.

The rotenone model of Parkinson's disease: genes, environment and mitochondria.

Dysfunction of mitochondrial complex I and the proteasome: interactions between two biochemical deficits in a cellular model of Parkinson's disease.

Mechanism of toxicity of pesticides acting at complex I: relevance to environmental etiologies of Parkinson's disease.

Circadian rhythms of oxidative phosphorylation: effects of rotenone and melatonin on isolated rat brain mitochondria.

Critical role for microglial NADPH oxidase in rotenone-induced degeneration of dopaminergic neurons.

Effect of fraxetin and myricetin on rotenone-induced cytotoxicity in SH-SY5Y cells: comparison with N-acetylcysteine.

Ca<sup>2+</sup>-induced oxidative stress in brain mitochondria treated with the respiratory chain inhibitor rotenone.

Selective microglial activation in the rat rotenone model of Parkinson's disease.

Activation of mitochondrial ATP-sensitive potassium channels increases cell viability against rotenone-induced cell death.

Synergistic dopaminergic neurotoxicity of the pesticide rotenone and inflammogen lipopolysaccharide: relevance to the etiology of Parkinson's disease.

Chronic systemic complex I inhibition induces a hypokinetic multisystem degeneration in rats.

Mitochondrial complex inhibitors preferentially damage substantia nigra dopamine neurons in rat brain slices.

Subcutaneous rotenone exposure causes highly selective dopaminergic degeneration and alpha-synuclein aggregation.

Quantitative relationship between inhibition of respiratory complexes and formation of reactive oxygen species in isolated nerve terminals.

Prostaglandin A1 inhibits rotenone-induced apoptosis in SH-SY5Y cells.

Possible involvement of both mitochondria- and endoplasmic reticulum-dependent caspase pathways in rotenone-induced apoptosis in human neuroblastoma SH-SY5Y cells.

Rotenone destroys dopaminergic neurons and induces parkinsonian symptoms in rats.

Regulation of hydrogen peroxide production by brain mitochondria by calcium and Bax.

Chronic rotenone treatment induces behavioral effects but no pathological signs of parkinsonism in mice.

Activation of adenosine triphosphate-sensitive potassium channels confers protection against rotenone-induced cell death: therapeutic implications for Parkinson's disease.

Modifying effects of dietary capsaicin and rotenone on 4-nitroquinoline 1-oxide-induced rat tongue carcinogenesis.

Coenzyme Q cytoprotective mechanisms for mitochondrial complex I cytopathies involves NAD(P)H: quinone oxidoreductase 1(NQO1).

### **Cluster 7 – Cell Death, especially MPP-Induced**

mpp 5.3%, cell 5.1%, death 3.4%, oxid 3.3%, cell.death 2.7%, stress 2.1%, apoptosi 2.0%, induc 1.5%, gsh 1.5%, neuron 1.5%, oxidative.stress 1.4%, cultur 1.3%, caspas 1.3%, estrogen 1.1%, paraquat 1.1%, activ 1.0%, pc12 1.0%, dopaminerg 0.9%, flavonoid 0.9%, protect 0.9%

Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic neurons in models of Parkinson's disease.

Protective effect and mechanism of Ginkgo biloba leaf extracts for Parkinson disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Caspase-9 activation results in downstream caspase-8 activation and bid cleavage in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease.

Manganese induces endoplasmic reticulum (ER) stress and activates multiple caspases in nigral dopaminergic neuronal cells, SN4741.

Microglial activation and dopaminergic cell injury: an in vitro model relevant to Parkinson's disease.

Lifespan extension and rescue of spongiform encephalopathy in superoxide dismutase 2 nullizygous mice treated with superoxide dismutase-catalase mimetics.

Molecular neurotoxicological models of Parkinsonism: focus on genetic manipulation of mice.

A pivotal role of matrix metalloproteinase-3 activity in dopaminergic neuronal degeneration via microglial activation.

Flavonoids protect neuronal cells from oxidative stress by three distinct mechanisms.

Phenolic antioxidants attenuate neuronal cell death following uptake of oxidized low-density lipoprotein.

The parkinsonism-inducing drug 1-methyl-4-phenylpyridinium triggers intracellular dopamine oxidation. A novel mechanism of toxicity.



Developmental cell death in dopaminergic neurons of the substantia nigra of mice.

1-Methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol) is toxic to dopaminergic neuroblastoma SH-SY5Y cells via impairment of cellular energy metabolism.

Overproduction of Cu/Zn-superoxide dismutase or Bcl-2 prevents the brain mitochondrial respiratory dysfunction induced by glutathione depletion.

Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease.

Paraquat induced activation of transcription factor AP-1 and apoptosis in PC12 cells.

Isoquinoline derivatives as endogenous neurotoxins in the aetiology of Parkinson's disease.

Monoamine oxidases: from brain maps to physiology and transgenics to pathophysiology.

Neuronal life-and-death signaling, apoptosis, and neurodegenerative disorders.

Cytotoxic effects of repin, a principal sesquiterpene lactone of Russian knapweed.

Transgenic murine dopaminergic neurons expressing human Cu/Zn superoxide dismutase exhibit increased density in culture, but no resistance to methylphenylpyridinium-induced degeneration.

Metallothioneins 1 and 2 attenuate peroxynitrite-induced oxidative stress in Parkinson disease.

Complex I inhibitors induce dose-dependent apoptosis in PC12 cells: relevance to Parkinson's disease.

[Transgenic mice overexpressing copper-zinc superoxide dismutase: a model for the study of radical mechanisms and aging]

Gene transfer of a reserpine-sensitive mechanism of resistance to N-methyl-4-phenylpyridinium.

Interaction of 1-methyl-4-phenylpyridinium ion with human platelets.

Energy-dependent uptake of N-methyl-4-phenylpyridinium, the neurotoxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, by mitochondria.

Ferritin oxidation and proteasomal degradation: protection by antioxidants.

Methoxyflavones protect cells against endoplasmic reticulum stress and neurotoxin.

Protective activities of Vaccinium antioxidants with potential relevance to mitochondrial dysfunction and neurotoxicity.

*Caenorhabditis elegans* MPP<sup>+</sup> model of Parkinson's disease for high-throughput drug screenings.

Mutational analysis of DJ-1 in *Drosophila* implicates functional inactivation by oxidative damage and aging.

Prominent corticosteroid disturbance in experimental prion disease.

Protocatechuic acid suppresses MPP<sup>+</sup> -induced mitochondrial dysfunction and apoptotic cell death in PC12 cells.

Progressive dopamine neuron loss in Parkinson's disease: the multiple hit hypothesis.

Midbrain neuronal cultures from parkin mutant mice are resistant to nitric oxide-induced toxicity.

Proteomic identification of a stress protein, mortalin/mthsp70/GRP75: relevance to Parkinson disease.

Enhancement of neuroprotection of mulberry leaves (*Morus alba* L.) prepared by the anaerobic treatment against ischemic damage.

Prevention of oxidative injury by flavonoids from stems and leaves of *Scutellaria baicalensis* Georgi in PC12 cells.

Baicalein attenuates 6-hydroxydopamine-induced neurotoxicity in SH-SY5Y cells.

Regulation of p53 by activated protein kinase C-delta during nitric oxide-induced dopaminergic cell death.

Protective effects of hyperoside (quercetin-3-o-galactoside) to PC12 cells against cytotoxicity induced by hydrogen peroxide and tert-butyl hydroperoxide.

Protocatechuic acid from *Alpinia oxyphylla* against MPP<sup>+</sup>-induced neurotoxicity in PC12 cells.

Heat shock proteins protect both MPP(+) and paraquat neurotoxicity.

Biochanin A protects dopaminergic neurons against lipopolysaccharide-induced damage through inhibition of microglia activation and proinflammatory factors generation.

*Drosophila* DJ-1 mutants are selectively sensitive to environmental toxins associated with Parkinson's disease.

CHOP/GADD153 is a mediator of apoptotic death in substantia nigra dopamine neurons in an in vivo neurotoxin model of parkinsonism.

Sgk1, a cell survival response in neurodegenerative diseases.

The role of microglia in paraquat-induced dopaminergic neurotoxicity.

Role of oxidative stress in paraquat-induced dopaminergic cell degeneration.

Overexpression of superoxide dismutase or glutathione peroxidase protects against the paraquat + maneb-induced Parkinson disease phenotype.

Microglial NADPH oxidase is a novel target for femtomolar neuroprotection against oxidative stress.

Femtomolar concentrations of dextromethorphan protect mesencephalic dopaminergic neurons from inflammatory damage.

Manganese superoxide dismutase protects against 6-hydroxydopamine injury in mouse brains.

The gestational environment and Parkinson's disease: evidence for neurodevelopmental origins of a neurodegenerative disorder.

A synthetic derivative of the natural product rocaglaol is a potent inhibitor of cytokine-mediated signaling and shows neuroprotective activity in vitro and in animal models of Parkinson's disease and traumatic brain injury.

Genistein protects dopaminergic neurons by inhibiting microglial activation.

Distinct mechanistic roles of calpain and caspase activation in neurodegeneration as revealed in mice overexpressing their specific inhibitors.

Inhibition of cyclin-dependent kinases is neuroprotective in 1-methyl-4-phenylpyridinium-induced apoptosis in neurons.

Ibuprofen and apigenin induce apoptosis and cell cycle arrest in activated microglia.

Dietary polyphenols protect dopamine neurons from oxidative insults and apoptosis: investigations in primary rat mesencephalic cultures.

Estradiol and raloxifene protect cultured SN4741 neurons against oxidative stress.

Neuroprotective role of the Reaper-related serine protease HtrA2/Omi revealed by targeted deletion in mice.

Inhibition of microglial activation by the herbal flavonoid baicalein attenuates inflammation-mediated degeneration of dopaminergic neurons.

Role of extracellular signal-regulated protein kinase in neuronal cell death induced by glutathione depletion in neuron/glia mesencephalic cultures.

Effects of dietary flavonoids on apoptotic pathways related to cancer chemoprevention.

Neuroprotective effects of *Hypericum perforatum* on trauma induced by hydrogen peroxide in PC12 cells.

Application of proteasomal inhibitors to mouse sympathetic neurons activates the intrinsic apoptotic pathway.

Salsolinol, a dopamine-derived tetrahydroisoquinoline, induces cell death by causing oxidative stress in dopaminergic SH-SY5Y cells, and the said effect is attenuated by metallothionein.

Inhibition of CDKs: a strategy for preventing kainic acid-induced apoptosis in neurons.

Effects of dopaminergic drugs on the mast cell degranulation and nitric oxide generation in RAW 264.7 cells.

Endogenous mitochondrial oxidative stress: neurodegeneration, proteomic analysis, specific respiratory chain defects, and efficacious antioxidant therapy in superoxide dismutase 2 null mice.

Estrogen, beta-amyloid metabolism/trafficking, and Alzheimer's disease.

Protective effect of sulforaphane against dopaminergic cell death.

NADPH oxidase mediates lipopolysaccharide-induced neurotoxicity and proinflammatory gene expression in activated microglia.

Targeted expression of BCL-2 attenuates MPP<sup>+</sup> but not 6-OHDA induced cell death in dopaminergic neurons.

Experimental study on the protective effect of puerarin to Parkinson disease.

Metallothionein attenuates 3-morpholinostyrene (SIN-1)-induced oxidative stress in dopaminergic neurons.

Ginsenoside Rg1 attenuates dopamine-induced apoptosis in PC12 cells by suppressing oxidative stress.

Models of Parkinson's disease.

Effects of estradiol, phytoestrogens, and Ginkgo biloba extracts against 1-methyl-4-phenyl-pyridine-induced oxidative stress.

BAK alters neuronal excitability and can switch from anti- to pro-death function during postnatal development.

Nitric oxide triggers the toxicity due to glutathione depletion in midbrain cultures through 12-lipoxygenase.

Effects of green tea polyphenols on dopamine uptake and on MPP<sup>+</sup>-induced dopamine neuron injury.

Endoplasmic reticulum stress and the unfolded protein response in cellular models of Parkinson's disease.

Tubuloside B from Cistanche salsa rescues the PC12 neuronal cells from 1-methyl-4-phenylpyridinium ion-induced apoptosis and oxidative stress.

Overexpression of midbrain-specific transcription factor Nurr1 modifies susceptibility of mouse neural stem cells to neurotoxins.

Control of oxidative stress resistance by IP3 kinase in *Drosophila melanogaster*.

Neuroprotective effect of estradiol and phytoestrogens on MPP<sup>+</sup>-induced cytotoxicity in neuronal PC12 cells.

Protective effect of verbascoside on 1-methyl-4-phenylpyridinium ion-induced neurotoxicity in PC12 cells.

Mitochondria determine the survival and death in apoptosis by an endogenous neurotoxin, N-methyl(R)salsolinol, and neuroprotection by propargylamines.

p53-dependent neuronal cell death in a DJ-1-deficient zebrafish model of Parkinson's disease.

Toxicity of Annonaceae for dopaminergic neurons: potential role in atypical parkinsonism in Guadeloupe.

### **Cluster 8 – Plant Extracts, especially Tea, for NeuroProtection**

ohda 12.4%, iron 8.4%, egcg 6.8%, glutathion 2.8%, tea 2.4%, neuroprotect 1.6%, chelat 1.6%, antioxid 1.5%, green.tea 1.4%, green 1.1%, cell 1.1%, polyphenol 1.1%, catechin 1.1%, oxid 1.0%, extract 0.9%, hydroxydopamin 0.8%, hydroxydopamine.ohda 0.8%, protect 0.7%, nrf2 0.7%, gallat 0.6%

Attenuation of 6-hydroxydopamine (6-OHDA)-induced nuclear factor-kappaB (NF-kappaB) activation and cell death by tea extracts in neuronal cultures.

Distinct effects of tea catechins on 6-hydroxydopamine-induced apoptosis in PC12 cells.

Different effects of five catechins on 6-hydroxydopamine-induced apoptosis in PC12 cells.

Tissue distribution and neuroprotective effects of citrus flavonoid tangeretin in a rat model of Parkinson's disease.

Green tea polyphenol (-)-epigallocatechin-3-gallate prevents N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced dopaminergic neurodegeneration.

The antioxidant activity of standardized extract of Ginkgo biloba (EGb 761) in rats.

Sustained extracellular signal-regulated kinase activation by 6-hydroxydopamine: implications for Parkinson's disease.

Neuroimmunophilin ligands exert neuroregeneration and neuroprotection in midbrain dopaminergic neurons.

Iron involvement in neural damage and microgliosis in models of neurodegenerative diseases.

Preferential resistance of dopaminergic neurons to the toxicity of glutathione depletion is independent of cellular glutathione peroxidase and is mediated by tetrahydrobiopterin.

Attenuation of 6-OHDA-induced neurotoxicity in glutathione peroxidase transgenic mice.



Excessive iron accumulation in the brain: a possible potential risk of neurodegeneration in Parkinson's disease.

Energy stress-induced dopamine loss in glutathione peroxidase-overexpressing transgenic mice and in glutathione-depleted mesencephalic cultures.

DJ-1, a cancer- and Parkinson's disease-associated protein, stabilizes the antioxidant transcriptional master regulator Nrf2.

RTP801 is elevated in Parkinson brain substantia nigral neurons and mediates death in cellular models of Parkinson's disease by a mechanism involving mammalian target of rapamycin inactivation.

Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: a review of their intracellular targets.

Protective effects of ethanolic extract of *Delphinium denudatum* in a rat model of Parkinson's disease.

Neural repair strategies for Parkinson's disease: insights from primate models.

Coenzyme Q(10) provides neuroprotection in iron-induced apoptosis in dopaminergic neurons.

Green tea catechins as brain-permeable, non toxic iron chelators to "iron out iron" from the brain.

Epigallocatechin gallate protects dopaminergic neurons against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity by inhibiting microglial cell activation.

Reduction of iron-regulated amyloid precursor protein and beta-amyloid peptide by (-)-epigallocatechin-3-gallate in cell cultures: implications for iron chelation in Alzheimer's disease.

Attenuation by *Nardostachys jatamansi* of 6-hydroxydopamine-induced parkinsonism in rats: behavioral, neurochemical, and immunohistochemical studies.

Neuroprotective and neurorescue effect of black tea extract in 6-hydroxydopamine-lesioned rat model of Parkinson's disease.

Green tea catechins as brain-permeable, natural iron chelators-antioxidants for the treatment of neurodegenerative disorders.

Toxin-induced models of Parkinson's disease.

Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease.

Protective effect of green tea polyphenols on the SH-SY5Y cells against 6-OHDA induced apoptosis through ROS-NO pathway.

Amburoside A, a glucoside from *Amburanacearensis*, protects mesencephalic cells against 6-hydroxydopamine-induced neurotoxicity.

Lentivirus-mediated expression of glutathione peroxidase: neuroprotection in murine models of Parkinson's disease.

Neuroprotection by crocetin in a hemi-parkinsonian rat model.

Multifunctional activities of green tea catechins in neuroprotection. Modulation of cell survival genes, iron-dependent oxidative stress and PKC signaling pathway.

Neuroprotective effects of *Withania somnifera* on 6-hydroxydopamine induced Parkinsonism in rats.

Ginkgo biloba affords dose-dependent protection against 6-hydroxydopamine-induced parkinsonism in rats: neurobehavioural, neurochemical and immunohistochemical evidences.

Nrf2-mediated protection against 6-hydroxydopamine.

(-)-Epigallocatechin gallate inhibits lipopolysaccharide-induced microglial activation and protects against inflammation-mediated dopaminergic neuronal injury.

Neuroprotective effect of Ginkgo biloba L. extract in a rat model of Parkinson's disease.

Iron-sulfur enzyme mediated mitochondrial superoxide toxicity in experimental Parkinson's disease.

Catechin polyphenols: neurodegeneration and neuroprotection in neurodegenerative diseases.

Selenium and brain function: a poorly recognized liaison.

The antioxidant drink effective microorganism-X (EM-X) pre-treatment attenuates the loss of nigrostriatal dopaminergic neurons in 6-hydroxydopamine-lesion rat model of Parkinson's disease.

Green tea polyphenol (-)-epigallocatechin-3-gallate protects rat PC12 cells from apoptosis induced by serum withdrawal independent of P13-Akt pathway.

Experimental excitotoxicity provokes oxidative damage in mice brain and attenuation by extract of Asparagus racemosus.

Catechin attenuates 6-hydroxydopamine (6-OHDA)-induced cell death in primary cultures of mesencephalic cells.

Interactions between environmental and genetic factors in the pathophysiology of Parkinson's disease.

Potential therapeutic properties of green tea polyphenols in Parkinson's disease.

Neuroprotective strategies in Parkinson's disease : an update on progress.

Gene and protein expression profiles of anti- and pro-apoptotic actions of dopamine, R-apomorphine, green tea polyphenol (-)-epigallocatechine-3-gallate, and melatonin.

Neuroprotection and neurorescue against Abeta toxicity and PKC-dependent release of nonamyloidogenic soluble precursor protein by green tea polyphenol (-)-epigallocatechin-3-gallate.

Genetic or pharmacological iron chelation prevents MPTP-induced neurotoxicity in vivo: a novel therapy for Parkinson's disease.

Ironic fate: can a banned drug control metal heavies in neurodegenerative diseases?

cDNA gene expression profile homology of antioxidants and their antiapoptotic and proapoptotic activities in human neuroblastoma cells.

Dose-dependent protective effect of selenium in rat model of Parkinson's disease: neurobehavioral and neurochemical evidences.

Prevention of nitric oxide-mediated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease in mice by tea phenolic epigallocatechin 3-gallate.

Differential modulation of growth and glutathione metabolism in cultured rat astrocytes by 4-hydroxynonenal and green tea polyphenol, epigallocatechin-3-gallate.

Protective effects of green tea polyphenols and their major component, (-)-epigallocatechin-3-gallate (EGCG), on 6-hydroxydopamine-induced apoptosis in PC12 cells.

Ceruloplasmin regulates iron levels in the CNS and prevents free radical injury.

Involvement of protein kinase C activation and cell survival/ cell cycle genes in green tea polyphenol (-)-epigallocatechin 3-gallate neuroprotective action.

## **Cluster 9 – Dopaminergic NeuroDegeneration, especially MPTP-**

### **Induced**

mptp 28.5%, mice 3.8%, methyl 1.7%, methyl.phenyl 1.6%, phenyl 1.5%, methyl.phenyl.tetrahydropyridine 1.5%, phenyl.tetrahydropyridine 1.5%, mptp.induced 1.5%, tetrahydropyridin 1.5%, tetrahydropyridine.mptp 1.2%, phenyl.tetrahydropyridine.mptp 1.2%, dopamin 1.2%, dopaminerg 1.2%, vmat2 1.1%, striatal 1.1%, tnfr 0.8%, induc 0.8%, inject 0.8%, neuron 0.6%, loss 0.6%

Chemokines in the MPTP model of Parkinson's disease: absence of CCL2 and its receptor CCR2 does not protect against striatal neurodegeneration.

Synthesis of 8-C-glucosylflavones.

Interactions of 1-methyl-4-phenylpyridinium and other compounds with P-glycoprotein: relevance to toxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Mice with very low expression of the vesicular monoamine transporter 2 gene survive into adulthood: potential mouse model for parkinsonism.

Neuroprotection by caffeine and A(2A) adenosine receptor inactivation in a model of Parkinson's disease.

Nerve growth factor prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced cell death via the Akt pathway by suppressing caspase-3-like activity using PC12 cells: relevance to therapeutical application for Parkinson's disease.

Mice with a partial deficiency of manganese superoxide dismutase show increased vulnerability to the mitochondrial toxins malonate, 3-nitropropionic acid, and MPTP.

NMDA but not non-NMDA excitotoxicity is mediated by Poly(ADP-ribose) polymerase.

Selenium deficiency potentiates methamphetamine-induced nigral neuronal loss; comparison with MPTP model.

Evidence for resistance to MPTP in C57BL/6 x BALB/c F1 hybrids as compared with their progenitor strains.

Enhanced N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in mice deficient in CuZn-superoxide dismutase or glutathione peroxidase.

Mice deficient in cellular glutathione peroxidase show increased vulnerability to malonate, 3-nitropropionic acid, and 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine.

Inducible nitric oxide synthase stimulates dopaminergic neurodegeneration in the MPTP model of Parkinson disease.

Poly(ADP-ribose) polymerase activation mediates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism.

Absence of MPTP-induced neuronal death in mice lacking the dopamine transporter.

Mice deficient in group IV cytosolic phospholipase A2 are resistant to MPTP neurotoxicity.

Attenuation of 6-hydroxydopamine-induced dopaminergic nigrostriatal lesions in superoxide dismutase transgenic mice.

Coenzyme Q10 attenuates the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced loss of striatal dopamine and dopaminergic axons in aged mice.

VMAT2 knockout mice: heterozygotes display reduced amphetamine-conditioned reward, enhanced amphetamine locomotion, and enhanced MPTP toxicity.

Nigral dopaminergic cell loss in vitamin E deficient rats.

Cytochrome P450 and Parkinson's disease: protective role of neuronal CYP 2E1 from MPTP toxicity.

The MPTP tale: pathway to prevention of Parkinson's disease?

Transgenic mice with increased Cu/Zn-superoxide dismutase activity are resistant to N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity.

Pyridine and other coal tar constituents as inhibitors of potato polyphenol oxidase: a non-animal model for neurochemical studies.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity: partial protection against striato-nigral dopamine depletion in C57BL/6J mice by cigarette smoke exposure and by beta-naphthoflavone-pretreatment.

Apparent unilateral visual neglect in MPTP-hemiparkinsonian monkeys is due to delayed initiation of motion.

Deficits in operant behaviour in monkeys treated with N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

2-Phenylpyridine and 3-phenylpyridine, constituents of tea, are unlikely to cause idiopathic Parkinson's disease.

Exposure to cigarette smoke does not decrease the neurotoxicity of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) does not destroy nigrostriatal neurons in the scorbutic guinea pig.

Dopaminergic neuronal loss in transgenic mice expressing the Parkinson's disease-associated UCH-L1 I93M mutant.

In vivo modulation of the Parkinsonian phenotype by Nrf2.

Effect of acute administration of hydroalcohol extract of *Ilex paraguariensis* St Hilaire (Aquifoliaceae) in animal models of Parkinson's disease.

Modeling neurodegenerative diseases in vivo review.

Uncoupling protein-2 promotes nigrostriatal dopamine neuronal function.

Enhanced neuroprotective effect by combination of bromocriptine and *Hypericum perforatum* extract against MPTP-induced neurotoxicity in mice.

Pharmacological activation of mGlu4 metabotropic glutamate receptors reduces nigrostriatal degeneration in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Reduced vesicular storage of dopamine causes progressive nigrostriatal neurodegeneration.

Adaptive acetylcholinesterase splicing patterns attenuate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinsonism in mice.

Genetic vitamin E deficiency does not affect MPTP susceptibility in the mouse brain.

Differential protection against MPTP or methamphetamine toxicity in dopamine neurons by deletion of ppN/OFQ expression.

gamma-Tocopherol attenuates MPTP-induced dopamine loss more efficiently than alpha-tocopherol in mouse brain.

Attenuation of MPTP-induced neurotoxicity and locomotor dysfunction in Nucling-deficient mice via suppression of the apoptosome pathway.

Neuroprotection by transgenic expression of glucose-6-phosphate dehydrogenase in dopaminergic nigrostriatal neurons of mice.

Granulocyte-colony stimulating factor is neuroprotective in a model of Parkinson's disease.

FGF-2 deficiency does not alter vulnerability of the dopaminergic nigrostriatal system towards MPTP intoxication in mice.

Effect of BR-16A (Mentat), a polyherbal formulation on drug-induced catalepsy in mice.

Enhanced de novo neurogenesis and dopaminergic neurogenesis in the substantia nigra of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease-like mice.

Increased vulnerability to L-DOPA toxicity in dopaminergic neurons From VMAT2 heterozygote knockout mice.



MTH1, an oxidized purine nucleoside triphosphatase, protects the dopamine neurons from oxidative damage in nucleic acids caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Dopamine depletion does not protect against acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in vivo.

Modulating effect of *Hypericum perforatum* extract on astrocytes in MPTP induced Parkinson's disease in mice.

Neuroprotective effects of *Polygonum multiflorum* on nigrostriatal dopaminergic degeneration induced by paraquat and maneb in mice.

Tumor necrosis factor-alpha receptor 1 (p55) knockout only transiently decreases the activation of c-Jun and does not affect the survival of axotomized dopaminergic nigral neurons.

Bone marrow-derived microglia contribute to the neuroinflammatory response and express iNOS in the MPTP mouse model of Parkinson's disease.

Ablation of the inflammatory enzyme myeloperoxidase mitigates features of Parkinson's disease in mice.

[Effect of the oil from *ganoderma lucidum* spores on pathological changes in the substantia nigra and behaviors of MPTP-treated mice]

Dietary restriction affects striatal glutamate in the MPTP-induced mouse model of nigrostriatal degeneration.

Involvement of interferon-gamma in microglial-mediated loss of dopaminergic neurons.

Uncoupling protein 2 protects dopaminergic neurons from acute 1,2,3,6-methyl-phenyl-tetrahydropyridine toxicity.

The pRb/E2F cell-cycle pathway mediates cell death in Parkinson's disease.

Hypersensitivity of DJ-1-deficient mice to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and oxidative stress.

Neuroprotective effects of echinacoside in the mouse MPTP model of Parkinson's disease.

*Acanthopanax senticosus* Harms as a prophylactic for MPTP-induced Parkinson's disease in rats.

Tumor necrosis factor- $\alpha$  receptor ablation in a chronic MPTP mouse model of Parkinson's disease.

Ginsenoside Rg1 reduces MPTP-induced substantia nigra neuron loss by suppressing oxidative stress.

Uncoupling protein-2 is critical for nigral dopamine cell survival in a mouse model of Parkinson's disease.

Reduced MPTP toxicity in noradrenaline transporter knockout mice.

Does ORP150/HSP12A protect dopaminergic neurons against MPTP/MPP(+)-induced neurotoxicity?

Low dose pramipexole is neuroprotective in the MPTP mouse model of Parkinson's disease, and downregulates the dopamine transporter via the D3 receptor.

An application of a new planar positron imaging system (PPIS) in a small animal: MPTP-induced parkinsonism in mouse.

Involvement of cytochrome P450 2E1 in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model of Parkinson's disease.

L-3-hydroxyacyl-CoA dehydrogenase II protects in a model of Parkinson's disease.

Neuroprotective effects of phenylethanoid glycosides from *Cistanches salsa* against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic toxicity in C57 mice.

Genetic ablation of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and pharmacological inhibition of TNF-synthesis attenuates MPTP toxicity in mouse striatum.

Prevention of MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) dopaminergic neurotoxicity in mice by chronic lithium: involvements of Bcl-2 and Bax.

Mice deficient in dihydrolipoamide dehydrogenase show increased vulnerability to MPTP, malonate and 3-nitropropionic acid neurotoxicity.

Regulation of dopaminergic loss by Fas in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease.

Caspase-11 mediates inflammatory dopaminergic cell death in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease.

GSTpi expression mediates dopaminergic neuron sensitivity in experimental parkinsonism.

Endogenous activation of mGlu5 metabotropic glutamate receptors contributes to the development of nigro-striatal damage induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice.

Behavioral effects of dopamine agonists and antagonists in MPTP-lesioned D3 receptor knockout mice.

Neuroprotective actions of the ginseng extract G115 in two rodent models of Parkinson's disease.

Glucocorticoid receptor deficiency increases vulnerability of the nigrostriatal dopaminergic system: critical role of glial nitric oxide.

Cyclin-dependent kinase 5 is a mediator of dopaminergic neuron loss in a mouse model of Parkinson's disease.

COX-2-deficient mice are less prone to MPTP-neurotoxicity than wild-type mice.

Temporal mRNA profiles of inflammatory mediators in the murine 1-methyl-4-phenyl-1,2,3,6-tetrahydropyrimidine model of Parkinson's disease.

Compromised reactive microgliosis in MPTP-lesioned IL-6 KO mice.

Critical role of microglial NADPH oxidase-derived free radicals in the in vitro MPTP model of Parkinson's disease.

[The effect of shourong compound formula on levels of dopamine and its metabolites in brain of Parkinson's disease mice induced by reserpine]

NADPH oxidase mediates oxidative stress in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease.

Attenuation of MPTP-induced neurotoxicity and behavioural impairment in NSE-XIAP transgenic mice.

Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration.

Role of TNF- $\alpha$  receptors in mice intoxicated with the parkinsonian toxin MPTP.

L-DOPA does not cause neurotoxicity in VMAT2 heterozygote knockout mice.

Localization and expression of group I metabotropic glutamate receptors in the mouse striatum, globus pallidus, and subthalamic nucleus: regulatory effects of MPTP treatment and constitutive Homer deletion.

Effect of complex phytoadaptogen on MPTP-induced Parkinson's syndrome in mice.

Role of Fc $\gamma$  receptors in nigral cell injury induced by Parkinson disease immunoglobulin injection into mouse substantia nigra.

Increased vulnerability of dopaminergic neurons in MPTP-lesioned interleukin-6 deficient mice.

Effect of tomato intake on striatal monoamine level in a mouse model of experimental Parkinson's disease.

Mice deficient in TNF receptors are protected against dopaminergic neurotoxicity: implications for Parkinson's disease.

8-(3-Chlorostyryl)caffeine may attenuate MPTP neurotoxicity through dual actions of monoamine oxidase inhibition and A2A receptor antagonism.

Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson disease.

### **Cluster 10 – Dopamine Receptors**

receptor 16.6%, dopamin 4.8%, mice 4.7%, a2a 2.1%, antagonist 1.5%, agonist 1.3%, d2r 1.2%, nicotin 1.0%, striatum 1.0%, locomotor 1.0%, dopamine.receptor 1.0%, behavior 0.9%, function 0.9%, nachr 0.9%, activ 0.9%, express 0.9%, knockout 0.8%, respons 0.8%, striatal 0.8%, d2l 0.7%

Persistent behavioral sensitization to chronic L-DOPA requires A2A adenosine receptors.

Dopamine as a prolactin (PRL) inhibitor.

Locomotor behavior of dopamine D1 receptor transgenic/D2 receptor deficient hybrid mice.

Neostriatal muscarinic receptor subtypes involved in the generation of tremulous jaw movements in rodents implications for cholinergic involvement in parkinsonism.

Dose-related neuroprotective effects of chronic nicotine in 6-hydroxydopamine treated rats, and loss of neuroprotection in alpha4 nicotinic receptor subunit knockout mice.

Dopamine-dependent synaptic plasticity in striatum during in vivo development.

Overexpression of the alpha1B-adrenergic receptor causes apoptotic neurodegeneration: multiple system atrophy.

Dopamine D2 long receptor-deficient mice display alterations in striatum-dependent functions.

The indirect basal ganglia pathway in dopamine D(2) receptor-deficient mice.

Rescue of locomotor impairment in dopamine D2 receptor-deficient mice by an adenosine A2A receptor antagonist.

Nicotine binding in human striatum: elevation in schizophrenia and reductions in dementia with Lewy bodies, Parkinson's disease and Alzheimer's disease and in relation to neuroleptic medication.

Nicotinic receptor subtypes in human brain ageing, Alzheimer and Lewy body diseases.

Cocaine reward and MPTP toxicity: alteration by regional variant dopamine transporter overexpression.

Differential regulation of tyrosine hydroxylase in the basal ganglia of mice lacking the dopamine transporter.

Dopamine D4 receptor-knock-out mice exhibit reduced exploration of novel stimuli.

Enhancement of D1 dopamine receptor-mediated locomotor stimulation in M(4) muscarinic acetylcholine receptor knockout mice.

Adaptive changes in postsynaptic dopamine receptors despite unaltered dopamine dynamics in mice lacking monoamine oxidase B.

New insights into dopaminergic receptor function using antisense and genetically altered animals.

[Behavioral, cellular and molecular consequences of the dopamine transporter gene inactivation]

Vitamin A functions in the regulation of the dopaminergic system in the brain and pituitary gland.

Rapid alterations in corticostriatal ensemble coordination during acute dopamine-dependent motor dysfunction.

Targeted expression of a toxin gene to D1 dopamine receptor neurons by cre-mediated site-specific recombination.

Dopaminergic control of sleep-wake states.

Impaired locomotion and dopamine signaling in retinoid receptor mutant mice.

The dopamine transporter: a crucial component regulating dopamine transmission.

Abnormal synaptic plasticity in the striatum of mice lacking dopamine D2 receptors.

[Dopamine control of neuroendocrine functions. New findings based on the study of transgenic animals]

Cellular and molecular aspects of monoamine neurotransmitter transporters.

DDD mice, a novel acute mouse model of Parkinson's disease.

Parkinsonian-like locomotor impairment in mice lacking dopamine D2 receptors.

Altered striatal function in a mutant mouse lacking D1A dopamine receptors.

Neurotrophins and ciliary neurotrophic factor: their biology and pathology.

CuZn-superoxide dismutase (CuZnSOD) transgenic mice show resistance to the lethal effects of methylenedioxymphetamine (MDA) and of methylenedioxymphetamine (MDMA).

Autoradiographic distribution of [3H]neurotensin receptors in the brains of superoxide dismutase transgenic mice.

Protein kinase C delta negatively regulates tyrosine hydroxylase activity and dopamine synthesis by enhancing protein phosphatase-2A activity in dopaminergic neurons.

Quantitative autoradiographic distribution of [3H]mazindol-labeled dopamine uptake sites in the brains of superoxide dismutase transgenic mice.

Age-dependent modulation of hippocampal long-term potentiation by antioxidant enzymes.

Behavioral phenotypes and pharmacology in genetic mouse models of Parkinsonism.



Impaired behavioural and molecular adaptations to dopamine denervation and repeated L-DOPA treatment in Nur77-knockout mice.

Nur77 gene knockout alters dopamine neuron biochemical activity and dopamine turnover.

New targets for pharmacological intervention in the glutamatergic synapse.

The high-affinity choline transporter: a critical protein for sustaining cholinergic signaling as revealed in studies of genetically altered mice.

RGS4-dependent attenuation of M4 autoreceptor function in striatal cholinergic interneurons following dopamine depletion.

Neurotransmitter depletion may be a cause of dementia pathology rather than an effect.

Locomotor activity is regulated by D2-like receptors in Drosophila: an anatomic and functional analysis.

When good Cdk5 turns bad.

[The mechanism of action of cannabis and cannabinoids]

Reversal of supersensitive striatal dopamine D1 receptor signaling and extracellular signal-regulated kinase activity in dopamine-deficient mice.

Lack of the DNA repair enzyme OGG1 sensitizes dopamine neurons to manganese toxicity during development.

Interactions between metabotropic glutamate 5 and adenosine A2A receptors in normal and parkinsonian mice.

JNK: bridging the insulin signaling and inflammatory pathway.

The dopamine D3 receptor antagonist NGB 2904 increases spontaneous and amphetamine-stimulated locomotion.

Blockade of nociceptin/orphanin FQ transmission attenuates symptoms and neurodegeneration associated with Parkinson's disease.

Neurochemical investigations of dopamine neuronal systems in iron-regulatory protein 2 (IRP-2) knockout mice.

Adenosine-dopamine interactions revealed in knockout mice.

Profound ataxia in complexin I knockout mice masks a complex phenotype that includes exploratory and habituation deficits.

Differential effects of l-DOPA on monoamine metabolism, cell survival and glutathione production in midbrain neuronal-enriched cultures from parkin knockout and wild-type mice.

Effects of cinnarizine, a calcium antagonist that produces human parkinsonism, in parkin knock out mice.

Cannabinoid CB(1) receptors in the basal ganglia and motor response to activation or blockade of these receptors in parkin-null mice.

Age-dependent motor deficits and dopaminergic dysfunction in DJ-1 null mice.

Involvement of cannabinoid receptors in the regulation of neurotransmitter release in the rodent striatum: a combined immunochemical and pharmacological analysis.

D3 dopamine receptors do not regulate neurogenesis in the subventricular zone of adult mice.

Critical involvement of cAMP/DARPP-32 and extracellular signal-regulated protein kinase signaling in L-DOPA-induced dyskinesia.

D2 dopamine receptors colocalize regulator of G-protein signaling 9-2 (RGS9-2) via the RGS9 DEP domain, and RGS9 knock-out mice develop dyskinesias associated with dopamine pathways.

Nigrostriatal dopaminergic deficits and hypokinesia caused by inactivation of the familial Parkinsonism-linked gene DJ-1.

Effects of age and dopamine D2L receptor-deficiency on motor and learning functions.

Neuroadaptations to hyperdopaminergia in dopamine D3 receptor-deficient mice.

[Are there innovations in the treatment of Parkinson's disease?]

Blockade of adenosine A2A receptors antagonizes parkinsonian tremor in the rat tacrine model by an action on specific striatal regions.

Dopaminergic properties and experimental anti-parkinsonian effects of IPX750 in rodent models of Parkinson disease.

M4 muscarinic receptors regulate the dynamics of cholinergic and dopaminergic neurotransmission: relevance to the pathophysiology and treatment of related CNS pathologies.

Immature nicastrin stabilizes A $\beta$ 1 independent of PEN-2 and presenilin: identification of nicastrin mutants that selectively interact with A $\beta$ 1.

Endocannabinoid-mediated rescue of striatal LTD and motor deficits in Parkinson's disease models.

Potential applications of nicotinic ligands in the laboratory and clinic.

Progressive sensorimotor impairment is not associated with reduced dopamine and high energy phosphate donors in a model of ataxia-telangiectasia.

Fibrillar amyloid protein present in atheroma activates CD36 signal transduction.

Progress in pursuit of therapeutic A2A antagonists: the adenosine A2A receptor selective antagonist KW6002: research and development toward a novel nondopaminergic therapy for Parkinson's disease.

Adenosine A2A receptors and depression.

Adenosine A2A receptors in neuroadaptation to repeated dopaminergic stimulation: implications for the treatment of dyskinesias in Parkinson's disease.

Altered striatal function and muscarinic cholinergic receptors in acetylcholinesterase knockout mice.

Stimulation of postsynaptic  $\alpha 1b$ - and  $\alpha 2$ -adrenergic receptors amplifies dopamine-mediated locomotor activity in both rats and mice.

Dopamine transporter: basic science and human variation of a key molecule for dopaminergic function, locomotion, and parkinsonism.

Distinct roles of D1 and D5 dopamine receptors in motor activity and striatal synaptic plasticity.

Subunit composition of functional nicotinic receptors in dopaminergic neurons investigated with knock-out mice.

Adenosine receptors as targets for drug development.

Corpus callosum and visual cortex of mice with deletion of the NMDA-NR1 receptor: I. Accelerated development of callosal projection neurons.

Group III metabotropic glutamate receptor-mediated modulation of the striatopallidal synapse.

Deficiency in Na,K-ATPase  $\alpha$  isoform genes alters spatial learning, motor activity, and anxiety in mice.

Nicotinic receptor mutant mice in the study of autonomic function.

Loss of anti-cataleptic effect of scopolamine in mice lacking muscarinic acetylcholine receptor subtype 4.

Dopaminergic supersensitivity in G protein-coupled receptor kinase 6-deficient mice.

Normal nigrostriatal innervation but dopamine dysfunction in mice carrying hypomorphic tyrosine hydroxylase alleles.

Motor dysfunction in type 5 adenylyl cyclase-null mice.

Alterations in D1/D2 synergism may account for enhanced stereotypy and reduced climbing in mice lacking dopamine D2L receptor.

D5 (not D1) dopamine receptors potentiate burst-firing in neurons of the subthalamic nucleus by modulating an L-type calcium conductance.

Adenosine receptor blockade reverses hypophagia and enhances locomotor activity of dopamine-deficient mice.

Forebrain adenosine A2A receptors contribute to L-3,4-dihydroxyphenylalanine-induced dyskinesia in hemiparkinsonian mice.

Mouse brains deficient in H-ferritin have normal iron concentration but a protein profile of iron deficiency and increased evidence of oxidative stress.

Dopamine D2S and D2L receptors may differentially contribute to the actions of antipsychotic and psychotic agents in mice.

Protein kinase C gamma (PKC gamma): function of neuron specific isotype.

Effects of long-term treatment with dopamine receptor agonists and antagonists on terminal arbor size.

Presenilin-dependent intramembrane proteolysis of CD44 leads to the liberation of its intracellular domain and the secretion of an Abeta-like peptide.

PEN-2 is an integral component of the gamma-secretase complex required for coordinated expression of presenilin and nicastrin.

Model mice for tissue-specific deletion of the manganese superoxide dismutase (MnSOD) gene.

Motor and associative deficits in D2 dopamine receptor knockout mice.

Possible anti-Parkinson properties of N-(alpha-linolenoyl) tyrosine: a new molecule.

Brain catecholamine metabolism in catechol-O-methyltransferase (COMT)-deficient mice.

### **Cluster 11 – Derived Neurotrophic Factors**

gdnf 10.2%, neuron 4.4%, midbrain 4.0%, nurr1 3.9%, bdnf 2.4%, ventral 2.2%, snc 2.0%, dopaminerg 1.8%, express 1.4%, dopaminergic.neurons 1.4%, nigra 1.3%, substantia 1.3%, mice 1.2%, substantia.nigra 1.2%, surviv 1.1%, neurotroph 1.1%, engrail 1.0%, fgf 1.0%, brain 0.9%, ventral.midbrain 0.8%

Marked dopaminergic cell loss subsequent to developmental, intranigral expression of glial cell line-derived neurotrophic factor.

Striatal dopamine output is compromised within +/- BDNF mice.

Impaired water maze learning performance without altered dopaminergic function in mice heterozygous for the GDNF mutation.

Selective enrichment of DJ-1 protein in primate striatal neuronal processes: implications for Parkinson's disease.

Fate of midbrain dopaminergic neurons controlled by the engrailed genes.

Morphological abnormalities in the brains of estrogen receptor beta knockout mice.

Nigrostriatal dopaminergic neurodegeneration in the weaver mouse is mediated via neuroinflammation and alleviated by minocycline administration.

Nigrostriatal innervation is preserved in Nurr1-null mice, although dopaminergic neuron precursors are arrested from terminal differentiation.

RET is dispensable for maintenance of midbrain dopaminergic neurons in adult mice.

Selective agenesis of mesencephalic dopaminergic neurons in Nurr1-deficient mice.

GDNF: a novel factor with therapeutic potential for neurodegenerative disorders.

Alternative sulfonylurea receptor expression defines metabolic sensitivity of K-ATP channels in dopaminergic midbrain neurons.

Neuroprotection and neuronal differentiation studies using substantia nigra dopaminergic cells derived from transgenic mouse embryos.

New evidence for presence of tyrosinase in substantia nigra, forebrain and midbrain.

Efferent projections of the retrorubral nucleus to the substantia nigra and ventral tegmental area in cats as shown by anterograde tracing.

Chronic dietary pergolide preserves nigrostriatal neuronal integrity in aged-Fischer-344 rats.

Slow progressive degeneration of nigral dopaminergic neurons in postnatal Engrailed mutant mice.

Mitochondria mass is low in mouse substantia nigra dopamine neurons: implications for Parkinson's disease.

VIP is a transcriptional target of Nurr1 in dopaminergic cells.

A partial GDNF depletion leads to earlier age-related deterioration of motor function and tyrosine hydroxylase expression in the substantia nigra.

Strategies to unravel molecular codes essential for the development of meso-diencephalic dopaminergic neurons.

Tomoregulin-2 is found extensively in plaques in Alzheimer's disease brain.

Chronic ferritin expression within murine dopaminergic midbrain neurons results in a progressive age-related neurodegeneration.

Genetic mouse models of parkinsonism: strengths and limitations.

A Wnt1-regulated genetic network controls the identity and fate of midbrain-dopaminergic progenitors in vivo.

K-ATP channels promote the differential degeneration of dopaminergic midbrain neurons.



Signalling through phospholipase C beta 4 is not essential for midbrain dopaminergic neuron survival.

Brain mitochondria contain aquaporin water channels: evidence for the expression of a short AQP9 isoform in the inner mitochondrial membrane.

Brain-derived neurotrophic factor is required for the establishment of the proper number of dopaminergic neurons in the substantia nigra pars compacta.

Electron tomography of degenerating neurons in mice with abnormal regulation of iron metabolism.

Degeneration of dopaminergic neurons in the substantia nigra of zitter mutant rat and protection by chronic intake of Vitamin E.

Selective glial cell line-derived neurotrophic factor production in adult dopaminergic carotid body cells in situ and after intrastriatal transplantation.

Evidence of a breakdown of corticostriatal connections in Parkinson's disease.

Effects of subchronic exposures to concentrated ambient particles. VII. Degeneration of dopaminergic neurons in Apo E<sup>-/-</sup> mice.

Maturation but not survival of dopaminergic nigrostriatal neurons is affected in developing and aging BDNF-deficient mice.

Viral vector mediated overexpression of human alpha-synuclein in the nigrostriatal dopaminergic neurons: a new model for Parkinson's disease.

Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease.

Age-dependent dopaminergic dysfunction in Nurr1 knockout mice.

The neuregulin receptor, ErbB4, is not required for normal development and adult maintenance of the substantia nigra pars compacta.

Regulation of the development of mesencephalic dopaminergic systems by the selective expression of glial cell line-derived neurotrophic factor in their targets.

Identification and developmental analysis of genes expressed by dopaminergic neurons of the substantia nigra pars compacta.

Structural determinants of heparan sulphate modulation of GDNF signalling.

Involvement of Nurr1 in specifying the neurotransmitter identity of ventral midbrain dopaminergic neurons.

[Regulation of estrogen and phytoestrogen on the dopaminergic systems of amygdala in rats]

High and complementary expression patterns of alcohol and aldehyde dehydrogenases in the gastrointestinal tract: implications for Parkinson's disease.

'Rejuvenation' protects neurons in mouse models of Parkinson's disease.

Selective loss of dopaminergic neurons in the substantia nigra of Pitx3-deficient aphakia mice.

Fibroblast growth factor (FGF)-2 and FGF receptor 3 are required for the development of the substantia nigra, and FGF-2 plays a crucial role for the rescue of dopaminergic neurons after 6-hydroxydopamine lesion.

Preferential neurotrophic activity of fibroblast growth factor-20 for dopaminergic neurons through fibroblast growth factor receptor-1c.

The control of dopamine neuron development, function and survival: insights from transgenic mice and the relevance to human disease.

Pitx3 is required for development of substantia nigra dopaminergic neurons.

An inflammatory review of Parkinson's disease.

Mutation of a putative nuclear receptor binding site abolishes activity of the nestin midbrain enhancer.

Neurotrophic and neuroprotective effects of tripchlorolide, an extract of Chinese herb *Tripterygium wilfordii* Hook F, on dopaminergic neurons.

JunB and Bcl-2 overexpression results in protection against cell death of nigral neurons following axotomy.

A role for TGF-beta signaling in neurodegeneration: evidence from genetically engineered models.

Effect of *Acanthopanax senticosus* Harms on biogenic monoamine levels in the rat brain.

Method for culturing postnatal substantia nigra as an in vitro model of experimental Parkinson's disease.

APP knockout attenuates microglial activation and enhances neuron survival in substantia nigra compacta after axotomy.

GDNF applied to the MPTP-lesioned nigrostriatal system requires TGF-beta for its neuroprotective action.

## **Cluster 12 – Cell Transplants and Grafting**

transplant 18.4%, graft 6.3%, cell 5.1%, gfp 3.3%, fetal 2.2%, embryon 2.0%, tissu 2.0%, surviv 1.9%, neural 1.8%, express 1.1%, transgen 1.0%, rat 0.9%, recipi 0.9%, host 0.9%, reject 0.9%, mice 0.8%, neuron 0.8%, differenti 0.8%, stem 0.7%, brain 0.7%

Phenotypic differentiation during migration of dopaminergic progenitor cells to the olfactory bulb.

Induction of a dopaminergic phenotype in cultured striatal neurons by bone morphogenetic proteins.

Enhanced axonal growth from fetal human bcl-2 transgenic mouse dopamine neurons transplanted to the adult rat striatum.

Generation of dopaminergic neurons in the adult brain from mesencephalic precursor cells labeled with a nestin-GFP transgene.

Visualization, direct isolation, and transplantation of midbrain dopaminergic neurons.

Neurobiology. Trigger found for synapse formation.

Xenotransplantation--state of the art--update 1999.

Somatic cell cloned transgenic bovine neurons for transplantation in parkinsonian rats.

Chimeric brain: theoretical and clinical aspects.

Implantation of xenogeneic transgenic neural plate tissues into parkinsonian rat brain.

Neuroectodermal grafting: a new tool for the study of neurodegenerative diseases.

Overexpressing Cu/Zn superoxide dismutase enhances survival of transplanted neurons in a rat model of Parkinson's disease.

Microglial chimaerism in human xenografts to the rat brain.

Nerve growth factor released by transgenic astrocytes enhances the function of adrenal chromaffin cell grafts in a rat model of Parkinson's disease.

Absence of MHC class II molecules reduces CNS demyelination, microglial/macrophage infiltration, and twitching in murine globoid cell leukodystrophy.

Age-related decline in the dopaminergic nigrostriatal system: the oxidative hypothesis and protective strategies.

Genes for human catecholamine-synthesizing enzymes.

Transplantation of fetal cells.

Control of peripheral nerve myelination by the beta-secretase BACE1.

Control of microglial neurotoxicity by the fractalkine receptor.

A method for a more complete in vitro Parkinson's model: slice culture bioassay for modeling maintenance and repair of the nigrostriatal circuit.

Purified mouse dopamine neurons thrive and function after transplantation into brain but require novel glial factors for survival in culture.

Effects of engrafted neural stem cells derived from GFP transgenic mice in Parkinson's diseases rats.

Generation and characterization of Sca2 (ataxin-2) knockout mice.

Sertoli cells improve survival of motor neurons in SOD1 transgenic mice, a model of amyotrophic lateral sclerosis.

Transplants of neurosphere cell suspensions from aged mice are functional in the mouse model of Parkinson's.

Purified mouse dopamine neurons thrive and function after transplantation into brain but require novel glial factors for survival in culture.

Silencing of the Pink1 gene expression by conditional RNAi does not induce dopaminergic neuron death in mice.

Identification of dopaminergic neurons of nigral and ventral tegmental area subtypes in grafts of fetal ventral mesencephalon based on cell morphology, protein expression, and efferent projections.

Functional properties and synaptic integration of genetically labelled dopaminergic neurons in intrastriatal grafts.

Tissue inhibitor of metalloproteinase-2 promotes neuronal differentiation by acting as an anti-mitogenic signal.

Gene-targeting technologies for the study of neurological disorders.

Neuroprotective properties of cultured neural progenitor cells are associated with the production of sonic hedgehog.

Characterization of five evolutionary conserved regions of the human tyrosine hydroxylase (TH) promoter: implications for the engineering of a human TH minimal promoter assembled in a self-inactivating lentiviral vector system.

Context-dependent neuronal differentiation and germ layer induction of Smad4<sup>-/-</sup> and Cripto<sup>-/-</sup> embryonic stem cells.

Sensitivity to oxidative stress in DJ-1-deficient dopamine neurons: an ES-derived cell model of primary Parkinsonism.

Fetal cell/tissue therapy in adult disease: a new horizon in regenerative medicine.

Molecular characterization of a thiJ-like gene in Chinese cabbage.

HIV-1 vectors: fulfillment of expectations, further advancements, and still a way to go.

Genetically engineered Sertoli cells are able to survive allogeneic transplantation.

Dietary supplementation with blueberry extract improves survival of transplanted dopamine neurons.

Establishment of modified chimeric mice using GFP bone marrow as a model for neurological disorders.

Immune parameters relevant to neural xenograft survival in the primate brain.

Intrastriatal grafting of glomus cells ameliorates behavioral defects of Parkinsonian rats.

Neuroprotective and neurorestorative signal transduction mechanisms in brain aging: modification by genes, diet and behavior.

Xenografts of MHC-deficient mouse embryonic mesencephalon improve behavioral recovery in hemiparkinsonian rats.

Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior.

Simultaneous inhibition of B7 and LFA-1 signaling prevents rejection of discordant neural xenografts in mice lacking CD40L.

### **Cluster 13 – Genetic Causes, especially Parkin Gene Mutations**

parkin 43.3%, ubiquitin 2.9%, protein 2.8%, mutant 1.1%, drosophila 1.1%, mutat 1.0%, function 0.9%, ligas 0.9%, degrad 0.8%, pink1 0.8%, aggreg 0.8%, polyglutamin 0.8%, gene 0.7%, rbr 0.7%, recess 0.6%, proteasom 0.6%, autosomal.recessive 0.6%, ubiquitin.ligase 0.6%, autosom 0.6%, substrat 0.6%

The septin CDCrel-1 is dispensable for normal development and neurotransmitter release.

Parkin and the molecular pathways of Parkinson's disease.

Over-expression of inducible HSP70 chaperone suppresses neuropathology and improves motor function in SCA1 mice.

Immunodetection of Parkin protein in vertebrate and invertebrate brains: a comparative study using specific antibodies.

Drosophila models of human neurodegenerative disease.

Role of DJ-1 in Parkinson's disease.

Identification of genes that modify ataxin-1-induced neurodegeneration.

Nuclear localization or inclusion body formation of ataxin-2 are not necessary for SCA2 pathogenesis in mouse or human.

Microtubule: a common target for parkin and Parkinson's disease toxins.

A ubiquitin ligase HRD1 promotes the degradation of Pael receptor, a substrate of Parkin.

Selective degeneration of Purkinje cells with Lewy body-like inclusions in aged NFHLACZ transgenic mice.

Eukaryotes have "two-component" signal transducers.

Structure and evolution of a multidomain multiphosphoryl transfer protein. Nucleotide sequence of the fruB(HI) gene in Rhodobacter capsulatus and comparisons with homologous genes from other organisms.



Loss of LRRK2/PARK8 induces degeneration of dopaminergic neurons in *Drosophila*.

Decline of striatal dopamine release in parkin-deficient mice shown by ex vivo autoradiography.

Antioxidants protect PINK1-dependent dopaminergic neurons in *Drosophila*.

Frameshift proteins in Alzheimer's disease and in other conformational disorders: time for the ubiquitin-proteasome system.

Comparative proteomics in neurodegenerative and non-neurodegenerative diseases suggest nodal point proteins in regulatory networking.

A regulated interaction with the UIM protein Eps15 implicates parkin in EGF receptor trafficking and PI(3)K-Akt signalling.

Mitochondrial pathology and muscle and dopaminergic neuron degeneration caused by inactivation of *Drosophila* Pink1 is rescued by Parkin.

Mutant alpha-synuclein-induced degeneration is reduced by parkin in a fly model of Parkinson's disease.

Mitochondrial dysfunction in *Drosophila* PINK1 mutants is complemented by parkin.

Identification of far upstream element-binding protein-1 as an authentic Parkin substrate.

Parkin protects against mitochondrial toxins and beta-amyloid accumulation in skeletal muscle cells.

Pathogenic chaperone-like RNA induces congophilic aggregates and facilitates neurodegeneration in *Drosophila*.

[Regulation of the protein degradation pathway by the ubiquitin family: its implication in neurodegenerative diseases]

Common structure and toxic function of amyloid oligomers implies a common mechanism of pathogenesis.

Comparative genomics and protein domain graph analyses link ubiquitination and RNA metabolism.

Lessons from *Drosophila* models of DJ-1 deficiency.

Parkin-deficient mice are not more sensitive to 6-hydroxydopamine or methamphetamine neurotoxicity.

Stress-induced alterations in parkin solubility promote parkin aggregation and compromise parkin's protective function.

Similar patterns of mitochondrial vulnerability and rescue induced by genetic modification of alpha-synuclein, parkin, and DJ-1 in *Caenorhabditis elegans*.

Overexpression of yeast hsp104 reduces polyglutamine aggregation and prolongs survival of a transgenic mouse model of Huntington's disease.

Proteomic analysis of parkin knockout mice: alterations in energy metabolism, protein handling and synaptic function.

Accumulation of the authentic parkin substrate aminoacyl-tRNA synthetase cofactor, p38/JTV-1, leads to catecholaminergic cell death.

Protein accumulation and neurodegeneration in the woozy mutant mouse is caused by disruption of SIL1, a cochaperone of BiP.

Dieldrin-induced neurotoxicity: relevance to Parkinson's disease pathogenesis.

Neurotoxicity and behavioral deficits associated with Septin 5 accumulation in dopaminergic neurons.

Accumulation of mutant neuroserpin precedes development of clinical symptoms in familial encephalopathy with neuroserpin inclusion bodies.

Yeast genome-wide screen reveals dissimilar sets of host genes affecting replication of RNA viruses.

A novel role for parkin in trauma-induced central nervous system secondary injury.

Autophagy is a prosurvival mechanism in cells expressing an autosomal dominant familial neurohypophyseal diabetes insipidus mutant vasopressin transgene.

Genetic and genomic studies of *Drosophila* parkin mutants implicate oxidative stress and innate immune responses in pathogenesis.

Parkin-deficient mice are not a robust model of parkinsonism.

MPTP and DSP-4 susceptibility of substantia nigra and locus coeruleus catecholaminergic neurons in mice is independent of parkin activity.

[Neurodegeneration caused by ER stress?--the pathogenetic mechanisms underlying AR-JP]

Structural determinants of the C-terminal helix-kink-helix motif essential for protein stability and survival promoting activity of DJ-1.

Dysregulation of stathmin, a microtubule-destabilizing protein, and up-regulation of Hsp25, Hsp27, and the antioxidant peroxiredoxin 6 in a mouse model of familial amyotrophic lateral sclerosis.

Microtubule disruption inhibits autophagosome-lysosome fusion: implications for studying the roles of aggresomes in polyglutamine diseases.

Nitrosative stress linked to sporadic Parkinson's disease: S-nitrosylation of parkin regulates its E3 ubiquitin ligase activity.

Loss of locus coeruleus neurons and reduced startle in parkin null mice.

How does parkin ligate ubiquitin to Parkinson's disease?

Parkin protects human dopaminergic neuroblastoma cells against dopamine-induced apoptosis.

Parkin and relatives: the RBR family of ubiquitin ligases.

S-nitrosylation of parkin regulates ubiquitination and compromises parkin's protective function.

Parkin counteracts symptoms in a *Drosophila* model of Parkinson's disease.

Mitochondrial dysfunction and oxidative damage in parkin-deficient mice.

It's a double knock-out! The quaking mouse is a spontaneous deletion of parkin and parkin co-regulated gene (PACRG).

Genetics of parkin-linked disease.

A *Drosophila* model of mutant human parkin-induced toxicity demonstrates selective loss of dopaminergic neurons and dependence on cellular dopamine.

Dopamine-dependent neurodegeneration in rats induced by viral vector-mediated overexpression of the parkin target protein, CDCrel-1.

Perturbed signal transduction in neurodegenerative disorders involving aberrant protein aggregation.

Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons.

Parkin gene inactivation alters behaviour and dopamine neurotransmission in the mouse.

A transgenic mouse model of the ubiquitin/proteasome system.

Protein transduction domain-mediated delivery of QBP1 suppresses polyglutamine-induced neurodegeneration in vivo.

Convergent pathobiologic model of Parkinson's disease.

Parkin facilitates the elimination of expanded polyglutamine proteins and leads to preservation of proteasome function.

Parkin suppresses dopaminergic neuron-selective neurotoxicity induced by Pael-R in *Drosophila*.

Comparative genomics of the RBR family, including the Parkinson's disease-related gene parkin and the genes of the ariadne subfamily.

### **Cluster 14 – Protein Tau Aggregations**

tau 51.5%, tauopathi 2.8%, ft dp 2.2%, mutat 1.3%, frontotemporal 1.2%, nft 1.2%, frontotemporal.dementia 1.1%, dementia 1.0%, dementia.parkinsonism 1.0%, filament 1.0%, p301l 0.9%, frontotemporal.dementia.parkinsonism 0.8%, abeta 0.8%, chromosom 0.7%, transgen 0.7%, linked.chromosome 0.7%, parkinsonism.linked.chromosome 0.7%, dementia.parkinsonism.linked 0.7%, parkinsonism.linked 0.7%, human.tau 0.6%

Neurodegeneration with tau accumulation in a transgenic mouse expressing V337M human tau.

FTDP-17 mutations in tau transgenic mice provoke lysosomal abnormalities and Tau filaments in forebrain.

Formation of filamentous tau aggregations in transgenic mice expressing V337M human tau.

Analysis of tauopathies with transgenic mice.

Gene expression profiling of the tau mutant (P301L) transgenic mouse brain.

Tau and transgenic animal models.

Oligodendroglial tau filament formation in transgenic mice expressing G272V tau.

Beta-amyloid treatment of two complementary P301L tau-expressing Alzheimer's disease models reveals similar deregulated cellular processes.

Attenuation of neurodegeneration-relevant modifications of brain proteins by dietary soy.

In vivo analysis of wild-type and FTDP-17 tau transgenic mice.

Tau filament formation in transgenic mice expressing P301L tau.

Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein.

Axonopathy and amyotrophy in mice transgenic for human four-repeat tau protein.

Prominent axonopathy in the brain and spinal cord of transgenic mice overexpressing four-repeat human tau protein.

Age-dependent emergence and progression of a tauopathy in transgenic mice overexpressing the shortest human tau isoform.

Chronic lithium administration to FTDP-17 tau and GSK-3 $\beta$  overexpressing mice prevents tau hyperphosphorylation and neurofibrillary tangle formation, but pre-formed neurofibrillary tangles do not revert.

5' splice site mutations in tau associated with the inherited dementia FTDP-17 affect a stem-loop structure that regulates alternative splicing of exon 10.

Alzheimer's disease and frontotemporal dementia: prospects of a tailored therapy?

Cortical neuronal and glial pathology in TgTauP301L transgenic mice: neuronal degeneration, memory disturbance, and phenotypic variation.

A decade of tau transgenic animal models and beyond.

Deletion of the ubiquitin ligase CHIP leads to the accumulation, but not the aggregation, of both endogenous phospho- and caspase-3-cleaved tau species.

The effects of sulfur amino acid intake on immune function in humans.

Suppression of Parkin enhances nigrostriatal and motor neuron lesion in mice over-expressing human-mutated tau protein.

Molecular pathways that influence human tau-induced pathology in *Caenorhabditis elegans*.

Improved long-term potentiation and memory in young tau-P301L transgenic mice before onset of hyperphosphorylation and tauopathy.

Impaired glutamate transport in a mouse model of tau pathology in astrocytes.

[Animal models of tauopathies]

Age-dependent neurofibrillary tangle formation, neuron loss, and memory impairment in a mouse model of human tauopathy (P301L).

Accumulation of pathological tau species and memory loss in a conditional model of tauopathy.

Progressive neurodegeneration in *C. elegans* model of tauopathy.

Enhanced neurofibrillary tangle formation, cerebral atrophy, and cognitive deficits induced by repetitive mild brain injury in a transgenic tauopathy mouse model.

Axonal degeneration induced by targeted expression of mutant human tau in oligodendrocytes of transgenic mice that model glial tauopathies.

Transgenic mice expressing mutant (N279K) human tau show mutation dependent cognitive deficits without neurofibrillary tangle formation.

Altered depression-related behavior and neurochemical changes in serotonergic neurons in mutant R406W human tau transgenic mice.

Current advances on different kinases involved in tau phosphorylation, and implications in Alzheimer's disease and tauopathies.

Neuroprotective effects of oral administration of triacetyluridine against MPTP neurotoxicity.

Proteomic and functional analyses reveal a mitochondrial dysfunction in P301L tau transgenic mice.

Transgenic mouse model of tau pathology in astrocytes leading to nervous system degeneration.

Accumulation of filamentous tau in the cerebral cortex of human tau R406W transgenic mice.

Stress kinases involved in tau phosphorylation in Alzheimer's disease, tauopathies and APP transgenic mice.



Tau alteration and neuronal degeneration in tauopathies: mechanisms and models.

Transgenic animal models of tauopathies.

Mutations causing neurodegenerative tauopathies.

Increased tau phosphorylation on mitogen-activated protein kinase consensus sites and cognitive decline in transgenic models for Alzheimer's disease and FTDP-17: evidence for distinct molecular processes underlying tau abnormalities.

CHIP-ping away at tau.

The role of tau (MAPT) in frontotemporal dementia and related tauopathies.

Transforming growth factor-beta signaling pathway as a therapeutic target in neurodegeneration.

Posttranslational modifications of tau--role in human tauopathies and modeling in transgenic animals.

[Animal models of neurodegenerative diseases]

Retarded axonal transport of R406W mutant tau in transgenic mice with a neurodegenerative tauopathy.

Olfactory dysfunction occurs in transgenic mice overexpressing human tau protein.

Tau protein and neurodegeneration.

Chronic lithium treatment decreases mutant tau protein aggregation in a transgenic mouse model.

Update on epidemiological aspects of progressive supranuclear palsy.

Neurodegeneration and defective neurotransmission in a *Caenorhabditis elegans* model of tauopathy.

Chaperones increase association of tau protein with microtubules.

Transgenic zebrafish model of neurodegeneration.

Abundant tau filaments and nonapoptotic neurodegeneration in transgenic mice expressing human P301S tau protein.

Modeling Alzheimer's disease and other proteopathies in vivo: is seeding the key?

Tau filament formation and associative memory deficit in aged mice expressing mutant (R406W) human tau.

[Analysis of mouse model exhibiting neurofibrillary changes]

Paradigm shifts in Alzheimer's disease and other neurodegenerative disorders: the emerging role of oligomeric assemblies.

Amyotrophic lateral sclerosis/parkinsonism dementia complex: transgenic mice provide insights into mechanisms underlying a common tauopathy in an ethnic minority on Guam.

Guadeloupean parkinsonism: a cluster of progressive supranuclear palsy-like tauopathy.

### **Cluster 15 – Alpha Synuclein Aggregation**

synuclein 24.6%, alpha.synuclein 20.1%, alpha 19.9%, aggreg 1.2%, lewi 0.9%, inclus 0.8%, transgen 0.8%, bodi 0.7%, express 0.6%, protein 0.6%, alphasyn 0.5%, mice 0.5%, a30p 0.4%, overexpress 0.4%, lewy.bodies 0.4%, human.alpha.synuclein 0.4%, human.alpha 0.4%, neuron 0.4%, mutant 0.3%, beta.synuclein 0.3%

Chaperone suppression of alpha-synuclein toxicity in a Drosophila model for Parkinson's disease.

Effects of pharmacological agents upon a transgenic model of Parkinson's disease in Drosophila melanogaster.

RNA interference-mediated knockdown of alpha-synuclein protects human dopaminergic neuroblastoma cells from MPP(+) toxicity and reduces dopamine transport.

Formation and removal of alpha-synuclein aggregates in cells exposed to mitochondrial inhibitors.

beta-Synuclein inhibits alpha-synuclein aggregation: a possible role as an anti-parkinsonian factor.

Membrane-bound alpha-synuclein has a high aggregation propensity and the ability to seed the aggregation of the cytosolic form.

beta-amyloid peptides enhance alpha-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease.

Transgenic invertebrate models of age-associated neurodegenerative diseases.

alpha-Synuclein occurs in lipid-rich high molecular weight complexes, binds fatty acids, and shows homology to the fatty acid-binding proteins.

Pesticides directly accelerate the rate of alpha-synuclein fibril formation: a possible factor in Parkinson's disease.

Sensitivity to MPTP is not increased in Parkinson's disease-associated mutant alpha-synuclein transgenic mice.

Experimental models of Parkinson's disease.

Mouse models of alpha-synucleinopathy and Lewy pathology.

Chronic systemic pesticide exposure reproduces features of Parkinson's disease.

Subcellular localization of wild-type and Parkinson's disease-associated mutant alpha -synuclein in human and transgenic mouse brain.

Neuropathology in mice expressing human alpha-synuclein.

Is there a cause-and-effect relationship between alpha-synuclein fibrillization and Parkinson's disease?

A Drosophila model of Parkinson's disease.

Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders.

TNF-alpha expressed in the brain of transgenic mice lowers central tyroxine hydroxylase immunoreactivity and alters grooming behavior.

Alpha-synuclein expression modulates microglial activation phenotype.

Pyrroloquinoline quinone (PQQ) prevents fibril formation of alpha-synuclein.

Alpha-synuclein acts in the nucleus to inhibit histone acetylation and promote neurotoxicity.

Beta-synuclein modulates alpha-synuclein neurotoxicity by reducing alpha-synuclein protein expression.

Alpha-synuclein overexpression increases cytosolic catecholamine concentration.

Behavioral effects of dopaminergic agonists in transgenic mice overexpressing human wildtype alpha-synuclein.

Mechanisms and models of alpha-synuclein-related neurodegeneration.

Cytosolic proteins regulate alpha-synuclein dissociation from presynaptic membranes.

Influence of different promoters on the expression pattern of mutated human alpha-synuclein in transgenic mice.

alpha-synuclein from platelets is not phosphorylated at serine 129 in Parkinson's disease and multiple system atrophy.

Linker histone H1 binds to disease associated amyloid-like fibrils.

Brain reward in the absence of alpha-synuclein.

Abnormal compartmentalization of norepinephrine in mouse dentate gyrus in alpha-synuclein knockout and A30P transgenic mice.

Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models.

Increased lifespan in transgenic *Caenorhabditis elegans* overexpressing human alpha-synuclein.

Identification of gene expression changes in transgenic *C. elegans* overexpressing human alpha-synuclein.

Pathological changes in dopaminergic nerve cells of the substantia nigra and olfactory bulb in mice transgenic for truncated human alpha-synuclein(1-120): implications for Lewy body disorders.

Inclusion body formation and neurodegeneration are parkin independent in a mouse model of alpha-synucleinopathy.

Proteasomal inhibition hypersensitizes differentiated neuroblastoma cells to oxidative damage.

Identification of rotenone-induced modifications in alpha-synuclein using affinity pull-down and tandem mass spectrometry.

Intersecting pathways to neurodegeneration in Parkinson's disease: effects of the pesticide rotenone on DJ-1, alpha-synuclein, and the ubiquitin-proteasome system.

Protein aggregation in retinal cells and approaches to cell protection.

High dose levodopa therapy is not toxic in multiple system atrophy: experimental evidence.

Alpha-synuclein is upregulated in neurones in response to chronic oxidative stress and is associated with neuroprotection.

Alpha-synuclein cooperates with CSPalpha in preventing neurodegeneration.

Familial Parkinson mutant alpha-synuclein causes dopamine neuron dysfunction in transgenic *Caenorhabditis elegans*.

Mitochondrial lipid abnormality and electron transport chain impairment in mice lacking alpha-synuclein.

Locomotor activity and evoked dopamine release are reduced in mice overexpressing A30P-mutated human alpha-synuclein.

Locomotor hyperactivity and alterations in dopamine neurotransmission are associated with overexpression of A53T mutant human alpha-synuclein in mice.

The mitochondrial complex I inhibitor rotenone triggers a cerebral tauopathy.

Evidence of oxidative stress in the neocortex in incidental Lewy body disease.

Alpha-synuclein transgenic mice: relevance to multiple system atrophy.

Animal models of multiple system atrophy.

Increased sensitivity to MPTP in human alpha-synuclein A30P transgenic mice.

The emerging utility of animal models of chronic neurodegenerative diseases.

Neuroprotection by iron chelator against proteasome inhibitor-induced nigral degeneration.

Alpha-synuclein gene deletion decreases brain palmitate uptake and alters the palmitate metabolism in the absence of alpha-synuclein palmitate binding.

Aggregated alpha-synuclein mediates dopaminergic neurotoxicity in vivo.

Rotenone induces aggregation of gamma-tubulin protein and subsequent disorganization of the centrosome: relevance to formation of inclusion bodies and neurodegeneration.

A precipitating role for truncated alpha-synuclein and the proteasome in alpha-synuclein aggregation: implications for pathogenesis of Parkinson disease.

Alpha-synuclein phosphorylation controls neurotoxicity and inclusion formation in a *Drosophila* model of Parkinson disease.

Torsin-mediated protection from cellular stress in the dopaminergic neurons of *Caenorhabditis elegans*.

Aggregated alpha-synuclein activates microglia: a process leading to disease progression in Parkinson's disease.

Lysosomal pathology associated with alpha-synuclein accumulation in transgenic models using an eGFP fusion protein.

Mitochondrial associated metabolic proteins are selectively oxidized in A30P alpha-synuclein transgenic mice--a model of familial Parkinson's disease.

Tau phosphorylation increases in symptomatic mice overexpressing A30P alpha-synuclein.

Iron and alpha-synuclein in the substantia nigra of MPTP-treated mice: effect of neuroprotective drugs R-apomorphine and green tea polyphenol (-)-epigallocatechin-3-gallate.

Exacerbated synucleinopathy in mice expressing A53T SNCA on a Snca null background.

Early and progressive sensorimotor anomalies in mice overexpressing wild-type human alpha-synuclein.

An antiaggregation gene therapy strategy for Lewy body disease utilizing beta-synuclein lentivirus in a transgenic model.

Alpha-synuclein and transgenic mouse models.

Double-knockout mice for alpha- and beta-synucleins: effect on synaptic functions.

Lack of alpha-synuclein does not alter apoptosis of neonatal catecholaminergic neurons.

Natural antioxidants and neurodegenerative diseases.

alpha-synuclein is required for the fibrillar nature of ubiquitinated inclusions induced by proteasomal inhibition in primary neurons.

Accumulation of beta- and gamma-synucleins in the ubiquitin carboxyl-terminal hydrolase L1-deficient gad mouse.

Mice lacking alpha-synuclein have an attenuated loss of striatal dopamine following prolonged chronic MPTP administration.

Lipid rafts mediate the synaptic localization of alpha-synuclein.

Analysis of alpha-synuclein-associated proteins by quantitative proteomics.

Developmental loss and resistance to MPTP toxicity of dopaminergic neurones in substantia nigra pars compacta of gamma-synuclein, alpha-synuclein and double alpha/gamma-synuclein null mutant mice.



Regional and progressive changes in brain expression of complexin II in a mouse transgenic for the Huntington's disease mutation.

Abnormal alpha-synuclein interactions with Rab proteins in alpha-synuclein A30P transgenic mice.

The flavonoid baicalein inhibits fibrillation of alpha-synuclein and disaggregates existing fibrils.

Hsp70 Reduces alpha-Synuclein Aggregation and Toxicity.

Enhanced substantia nigra mitochondrial pathology in human alpha-synuclein transgenic mice after treatment with MPTP.

Risk factors for dopaminergic neuron loss in human alpha-synuclein transgenic mice.

Pathological properties of the Parkinson's disease-associated protein DJ-1 in alpha-synucleinopathies and tauopathies: relevance for multiple system atrophy and Pick's disease.

Clearance of alpha-synuclein oligomeric intermediates via the lysosomal degradation pathway.

Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease.

Proteasome mediates dopaminergic neuronal degeneration, and its inhibition causes alpha-synuclein inclusions.

Molecular pathways of neurodegeneration in Parkinson's disease.

Transgenic mice expressing mutant A53T human alpha-synuclein show neuronal dysfunction in the absence of aggregate formation.

Alpha-synuclein expression in HEK293 cells enhances the mitochondrial sensitivity to rotenone.

Altered fatty acid composition of dopaminergic neurons expressing alpha-synuclein and human brains with alpha-synucleinopathies.

Pesticide exposure exacerbates alpha-synucleinopathy in an A53T transgenic mouse model.

Epitope mapping and specificity of the anti-alpha-synuclein monoclonal antibody Syn-1 in mouse brain and cultured cell lines.

Wild-type and mutant alpha-synuclein induce a multi-component gene expression profile consistent with shared pathophysiology in different transgenic mouse models of PD.

The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins?

Disease model: Parkinson's disease.

Gene expression changes presage neurodegeneration in a Drosophila model of Parkinson's disease.

Dopaminergic neuron loss and up-regulation of chaperone protein mRNA induced by targeted over-expression of alpha-synuclein in mouse substantia nigra.

Modeling CNS neurodegeneration by overexpression of disease-causing proteins using viral vectors.

Transgenic models of alpha-synuclein pathology: past, present, and future.

Ubiquitination of alpha-synuclein is not required for formation of pathological inclusions in alpha-synucleinopathies.

Dopaminergic neuronal loss and motor deficits in *Caenorhabditis elegans* overexpressing human alpha-synuclein.

Role of alpha-synuclein in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in mice.

Alpha-synuclein aggregation and neurodegenerative diseases.

Alpha-synuclein overexpression protects against paraquat-induced neurodegeneration.

[Genetics and environmental factors of Parkinson disease]

Protein expression in a *Drosophila* model of Parkinson's disease.

Altered short-term hippocampal synaptic plasticity in mutant alpha-synuclein transgenic mice.

The formation of highly soluble oligomers of alpha-synuclein is regulated by fatty acids and enhanced in Parkinson's disease.

Recent advances on alpha-synuclein cell biology: functions and dysfunctions.

Motor dysfunction and gliosis with preserved dopaminergic markers in human alpha-synuclein A30P transgenic mice.

Misfolded proteinase K-resistant hyperphosphorylated alpha-synuclein in aged transgenic mice with locomotor deterioration and in human alpha-synucleinopathies.

Development of new treatments for Parkinson's disease in transgenic animal models: a role for beta-synuclein.

Mice expressing the alpha(1B)-adrenergic receptor induces a synucleinopathy with excessive tyrosine nitration but decreased phosphorylation.

Synaptic vesicle depletion correlates with attenuated synaptic responses to prolonged repetitive stimulation in mice lacking alpha-synuclein.

Resistance of alpha-synuclein null mice to the parkinsonian neurotoxin MPTP.

Amyloid precursor protein, presenilins, and alpha-synuclein: molecular pathogenesis and pharmacological applications in Alzheimer's disease.

Alpha-synuclein regulates neuronal survival via Bcl-2 family expression and PI3/Akt kinase pathway.

Development of a new treatment for Alzheimer's disease and Parkinson's disease using anti-aggregatory beta-synuclein-derived peptides.

An in vitro model of Parkinson's disease: linking mitochondrial impairment to altered alpha-synuclein metabolism and oxidative damage.

Expression of mutant alpha-synucleins enhances dopamine transporter-mediated MPP<sup>+</sup> toxicity in vitro.

### **Cluster 16 – Alpha Synuclein Impacts**

syn 43.1%, alpha.syn 31.2%, alpha 10.3%, synuclein.alpha.syn 0.5%, alpha.synuclein.alpha 0.5%, synuclein.alpha 0.5%, halpha.syn 0.4%, synuclein 0.4%, halpha 0.3%, a53t 0.3%, aggreg 0.3%, mice 0.2%, alpha.synuclein 0.2%, synucleinopathi 0.2%, calpain 0.2%, accumul 0.2%, lewi 0.2%, proteasom 0.2%, inclus 0.2%, express 0.2%

Selective insolubility of alpha-synuclein in human Lewy body diseases is recapitulated in a transgenic mouse model.

Physiology and pathophysiology of alpha-synuclein. Cell culture and transgenic animal models based on a Parkinson's disease-associated protein.

Alpha-synuclein overexpression in PC12 and chromaffin cells impairs catecholamine release by interfering with a late step in exocytosis.

Alpha-synuclein induces hyperphosphorylation of Tau in the MPTP model of parkinsonism.

Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system.

Cytosolic catechols inhibit alpha-synuclein aggregation and facilitate the formation of intracellular soluble oligomeric intermediates.

Effects of the cholesterol-lowering compound methyl-beta-cyclodextrin in models of alpha-synucleinopathy.

Expression of alpha-synuclein, a presynaptic protein implicated in Parkinson's disease, in erythropoietic lineage.

Selective loss of dopaminergic neurons and formation of Lewy body-like aggregations in alpha-synuclein transgenic fly neuronal cultures.

Proteasome dysfunction in aged human alpha-synuclein transgenic mice.

Calpain-cleavage of alpha-synuclein: connecting proteolytic processing to disease-linked aggregation.

Convergence of heat shock protein 90 with ubiquitin in filamentous alpha-synuclein inclusions of alpha-synucleinopathies.

Parkinson's disease alpha-synuclein transgenic mice develop neuronal mitochondrial degeneration and cell death.

Neurological and neurodegenerative alterations in a transgenic mouse model expressing human alpha-synuclein under oligodendrocyte promoter: implications for multiple system atrophy.

Inhibition of alpha-synuclein fibrillization by dopamine analogs via reaction with the amino groups of alpha-synuclein. Implication for dopaminergic neurodegeneration.

Effects of alpha-synuclein immunization in a mouse model of Parkinson's disease.

Metallothionein-mediated neuroprotection in genetically engineered mouse models of Parkinson's disease.

Oxidative stress in transgenic mice with oligodendroglial alpha-synuclein overexpression replicates the characteristic neuropathology of multiple system atrophy.

Aggregation promoting C-terminal truncation of alpha-synuclein is a normal cellular process and is enhanced by the familial Parkinson's disease-linked mutations.

Stressor-related impairment of synaptic transmission in hippocampal slices from alpha-synuclein knockout mice.

alpha-Synuclein expression levels do not significantly affect proteasome function and expression in mice and stably transfected PC12 cell lines.

Transgenic mice with human mutant genes causing Parkinson's disease and amyotrophic lateral sclerosis provide common insight into mechanisms of motor neuron selective vulnerability to degeneration.

Stabilization of alpha-synuclein protein with aging and familial parkinson's disease-linked A53T mutation.

Alpha-synuclein: normal function and role in neurodegenerative diseases.

Axonal transport of human alpha-synuclein slows with aging but is not affected by familial Parkinson's disease-linked mutations.

Age-dependent synuclein pathology following traumatic brain injury in mice.

Fe(II)-induced DNA damage in alpha-synuclein-transfected human dopaminergic BE(2)-M17 neuroblastoma cells: detection by the Comet assay.

Distinct cleavage patterns of normal and pathologic forms of alpha-synuclein by calpain I in vitro.

alpha -Synucleinopathy and selective dopaminergic neuron loss in a rat lentiviral-based model of Parkinson's disease.

Human alpha-synuclein-harboring familial Parkinson's disease-linked Ala-53 --> Thr mutation causes neurodegenerative disease with alpha-synuclein aggregation in transgenic mice.

alpha-Synuclein, oxidative stress and apoptosis from the perspective of a yeast model of Parkinson's disease.

Hyperphosphorylation and insolubility of alpha-synuclein in transgenic mouse oligodendrocytes.

Behavioral and neurochemical effects of wild-type and mutated human alpha-synuclein in transgenic mice.

## APPENDIX 7 – ALZHEIMER’S DISEASE CORE LITERATURE

This appendix summarizes the Alzheimer’s Disease (AD) core literature restricted to select semantic classes. While this is not discovery, since AD is mentioned in each record, nevertheless, there is substantial value in collecting this information in one place. Due to time restrictions, we present article citations only.

The query used to retrieve the AD core literature was restricted to **non-drug** semantic classes, similar conceptually to what was used in Chapter 5. The main difference is that the query used for this appendix contained more non-drug semantic classes than was the case for Chapter 5, but a few less classes than was the case for Appendix 6.. The query used for this appendix may be written as:

(PLANTS, MEDICINAL [MH] OR PLANTS, EDIBLE [MH] OR "PLANT EXTRACTS" [MH] OR "PLANT PREPARATIONS" [MH] OR "PLANT OILS" [MH] OR PHYTOTHERAPY [MH] OR FRUIT [MH] OR VEGETABLES [MH] OR "FISH OILS" [MH] OR ALGAE [MH] OR NUTS [MH] OR "DAIRY PRODUCTS" [MH] OR FATS [MH] OR DIET [MH] OR FLAVONOIDS [MH] OR "DIETARY SUPPLEMENTS" [MH] OR Plants [MH] OR Plankton [MH] OR Plant Components [MH] OR Plant Families and Groups [MH] OR Seedling [MH] OR Trees [MH] OR Algae [MH] OR Algae, Brown [MH] OR Algae, Golden-Brown [MH] OR Algae, Green [MH] OR Algae, Red [MH] OR Lichens [MH] OR Seaweed [MH]) AND ALZHEIMER\*

where the non-drug phrases in CAPS are those used in the Chapter 5 core query, and the lower case phrases are those added for this appendix. There are undoubtedly more non-drug semantic classes that could be added, but we believe the present query provides a good representation of the total core AD non-drug literature.

We entered the query into the PubMed search engine, and retrieved 947 records with Abstracts. The citation for each of the 947 records is as follows:

1: Song C, Zhao S.



Omega-3 fatty acid eicosapentaenoic acid. A new treatment for psychiatric and neurodegenerative diseases: a review of clinical investigations. Expert Opin Investig Drugs. 2007 Oct;16(10):1627-38. Review. PMID: 17922626 [PubMed - indexed for MEDLINE]

2: Vafeiadou K, Vauzour D, Spencer JP. Neuroinflammation and its modulation by flavonoids. Endocr Metab Immune Disord Drug Targets. 2007 Sep;7(3):211-24. Review. PMID: 17897048 [PubMed - indexed for MEDLINE]

3: Scarmeas N, Luchsinger JA, Mayeux R, Stern Y. Mediterranean diet and Alzheimer disease mortality. Neurology. 2007 Sep 11;69(11):1084-93. PMID: 17846408 [PubMed - indexed for MEDLINE]

4: Kaplan M, Mutlu EA, Benson M, Fields JZ, Banan A, Keshavarzian A. Use of herbal preparations in the treatment of oxidant-mediated inflammatory disorders. Complement Ther Med. 2007 Sep;15(3):207-16. Epub 2006 Aug 21. Review. PMID: 17709066 [PubMed - indexed for MEDLINE]

5: Scripnikov A, Khomenko A, Napryeyenko O; GINDEM-NP Study Group. Effects of Ginkgo biloba extract EGb 761 on neuropsychiatric symptoms of dementia: findings from a randomised controlled trial. Wien Med Wochenschr. 2007;157(13-14):295-300. PMID: 17704975 [PubMed - indexed for MEDLINE]

6: Lee SH, Jun M, Choi JY, Yang EJ, Hur JM, Bae K, Seong YH, Huh TL, Song KS. Plant phenolics as prolyl endopeptidase inhibitors. Arch Pharm Res. 2007 Jul;30(7):827-33. PMID: 17703733 [PubMed - indexed for MEDLINE]

7: Vongpaseuth K, Roberts SC.

Advancements in the understanding of Paclitaxel metabolism in tissue culture.

Curr Pharm Biotechnol. 2007 Aug;8(4):219-36. Review.

PMID: 17691991 [PubMed - indexed for MEDLINE]

8: Gan L.

Therapeutic potential of sirtuin-activating compounds in Alzheimer's disease.

Drug News Perspect. 2007 May;20(4):233-9. Review.

PMID: 17637936 [PubMed - indexed for MEDLINE]

9: Huppert FA, Van Niekerk JK.

WITHDRAWN: Dehydroepiandrosterone (DHEA) supplementation for cognitive function.

Cochrane Database Syst Rev. 2007 Jul 18;(3):CD000304. Review.

PMID: 17636627 [PubMed - indexed for MEDLINE]

10: Balk E, Chung M, Raman G, Tatsioni A, Chew P, Ip S, DeVine D, Lau J.

B vitamins and berries and age-related neurodegenerative disorders.

Evid Rep Technol Assess (Full Rep). 2006 Apr;(134):1-161. Review.

PMID: 17628125 [PubMed - indexed for MEDLINE]

11: Ramassamy C, Longpre F, Christen Y.

Ginkgo biloba extract (EGb 761) in Alzheimer's disease: is there any evidence?

Curr Alzheimer Res. 2007 Jul;4(3):253-62. Review.

PMID: 17627482 [PubMed - indexed for MEDLINE]

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Effect of folate oversupplementation on folate uptake by human intestinal and

renal epithelial cells.

Am J Clin Nutr. 2007 Jul;86(1):159-66.

PMID: 17616776 [PubMed - indexed for MEDLINE]

13: Lau FC, Shukitt-Hale B, Joseph JA.

Nutritional intervention in brain aging: reducing the effects of inflammation and

oxidative stress.

Subcell Biochem. 2007;42:299-318. Review.

PMID: 17612057 [PubMed - indexed for MEDLINE]

14: Dosunmu R, Wu J, Basha MR, Zawia NH.

Environmental and dietary risk factors in Alzheimer's disease.

Expert Rev Neurother. 2007 Jul;7(7):887-900. Review.

PMID: 17610395 [PubMed - indexed for MEDLINE]

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J Agric Food Chem. 2007 Jul 25;55(15):6000-6. Epub 2007 Jun 28.

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Adv Exp Med Biol. 2007;595:1-75. Review.

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Distinct profiles of alpha7 nAChR positive allosteric modulation revealed by

structurally diverse chemotypes.

Mol Pharmacol. 2007 Sep;72(3):715-24. Epub 2007 Jun 12.

PMID: 17565004 [PubMed - indexed for MEDLINE]

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[A possible influence of nutrient factors in the mechanism development of the

neurodegenerative diseases--alzheimer's disease and spongiform encephalopathy

with people]

Vopr Pitan. 2007;76(2):39-44. Review. Russian.

PMID: 17561654 [PubMed - indexed for MEDLINE]

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Resveratrol oligomers from Vitis amurensis attenuate beta-amyloid-induced

oxidative stress in PC12 cells.

Biol Pharm Bull. 2007 Jun;30(6):1130-4.

PMID: 17541166 [PubMed - indexed for MEDLINE]

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3,4-dihydroxybenzoic acid from *Smilacis chinae* rhizome protects amyloid beta

protein (25-35)-induced neurotoxicity in cultured rat cortical neurons.

Neurosci Lett. 2007 Jun 13;420(2):184-8. Epub 2007 May 10.

PMID: 17531386 [PubMed - indexed for MEDLINE]

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Mitochondrial oxidant signalling in Alzheimer's disease.

J Alzheimers Dis. 2007 May;11(2):175-81. Review.

PMID: 17522442 [PubMed - indexed for MEDLINE]

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Glycemic load and risk of Alzheimer's disease.

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PMID: 17508100 [PubMed - indexed for MEDLINE]

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Folate deprivation increases presenilin expression, gamma-secretase activity, and

Abeta levels in murine brain: potentiation by ApoE deficiency and alleviation by

dietary S-adenosyl methionine.

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Transport of cryptotanshinone, a major active triterpenoid in *Salvia miltiorrhiza*

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blood-brain barrier.

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LPS-stimulated microglia by methanol extract of Phellodendri cortex.  
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Is antioxidant therapy a viable alternative for mild cognitive impairment?  
Examination of the evidence.  
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Plants in treating senile dementia in the northwest Amazon.  
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Biol Chem Hoppe Seyler. 1992 Oct;373(10):1075-8.

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[Effect of yizhiling granule on experimental pathological model of Alzheimer's disease]

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PMID: 1302548 [PubMed - indexed for MEDLINE]

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Amyloidogenicity of beta A4 and beta A4-bearing amyloid protein precursor fragments by metal-catalyzed oxidation.

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Acta Neurol (Napoli). 1992 Aug-Dec;14(4-6):455-68. Review.

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Aluminium beverage cans as a dietary source of aluminium.

Med J Aust. 1992 May 4;156(9):604-5.

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[Development of physostigmine from a poisonous plant to an antidote. One of the

most important drugs in the development of modern medicine?]

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PMID: 1579914 [PubMed - indexed for MEDLINE]

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A review of magnesium intake in the elderly. A cause for concern?

Magnes Res. 1992 Mar;5(1):61-7. Review.

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Nutritional patterns and weight change in Alzheimer patients.

Int Psychogeriatr. 1992 Summer;4(1):103-18.

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Factors affecting food intake of women with Alzheimer's type dementia in long-term care.

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Metabolic changes in Alzheimer's disease.  
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Why are Alzheimer patients thin?  
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Guam ALS/parkinsonism-dementia: a long-latency neurotoxic disorder caused by



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Can J Neurol Sci. 1987 Aug;14(3 Suppl):347-57. Review.

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PMID: 3453743 [PubMed - indexed for MEDLINE]

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J Am Geriatr Soc. 1987 Jan;35(1):31-8.

PMID: 3098821 [PubMed - indexed for MEDLINE]

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[Treatment of the disorders of aging with Ginkgo biloba extract. From pharmacology to clinical medicine]

Presse Med. 1986 Sep 25;15(31):1540-5. Review. French.

PMID: 3024145 [PubMed - indexed for MEDLINE]

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[Effect of Ginkgo biloba extract on the hemato-encephalic barrier]

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PMID: 3024144 [PubMed - indexed for MEDLINE]

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[Methodology for a controlled trial in Alzheimer's disease]

Presse Med. 1986 Sep 25;15(31):1577-82. French.

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PMID: 3910309 [PubMed - indexed for MEDLINE]
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PMID: 3966587 [PubMed - indexed for MEDLINE]
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PMID: 6350535 [PubMed - indexed for MEDLINE]
- 946: Wood JL, Allison RG.  
Effects of consumption of choline and lecithin on neurological and cardiovascular

systems.

Fed Proc. 1982 Dec;41(14):3015-21. Review.

PMID: 6754453 [PubMed - indexed for MEDLINE]

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Dietary aluminum and Alzheimer's disease--a review.

Sci Total Environ. 1981 Jan;17(1):31-6. Review.

PMID: 7010599 [PubMed - indexed for MEDLINE]

## APPENDIX 8 – PARKINSON’S DISEASE CORE LITERATURE

This appendix summarizes the PD core literature restricted to select semantic classes. While this is not discovery, since PD is mentioned in each record, nevertheless, there is substantial value in collecting this information in one place. Due to time restrictions, we present article citations only.

The query used to retrieve the PD core literature was restricted to **non-drug** semantic classes, similar conceptually to what was used in Chapter 5. The main difference is that the query used for this appendix contained more non-drug semantic classes than was the case for Chapter 5, but a few less classes than was the case for Appendix 6.. The query used for this appendix may be written as:

(PLANTS, MEDICINAL [MH] OR PLANTS, EDIBLE [MH] OR "PLANT EXTRACTS" [MH] OR "PLANT PREPARATIONS" [MH] OR "PLANT OILS" [MH] OR PHYTOTHERAPY [MH] OR FRUIT [MH] OR VEGETABLES [MH] OR "FISH OILS" [MH] OR ALGAE [MH] OR NUTS [MH] OR "DAIRY PRODUCTS" [MH] OR FATS [MH] OR DIET [MH] OR FLAVONOIDS [MH] OR "DIETARY SUPPLEMENTS" [MH] OR Plants [MH] OR Plankton [MH] OR Plant Components [MH] OR Plant Families and Groups [MH] OR Seedling [MH] OR Trees [MH] OR Algae [MH] OR Algae, Brown [MH] OR Algae, Golden-Brown [MH] OR Algae, Green [MH] OR Algae, Red [MH] OR Lichens [MH] OR Seaweed [MH]) AND (Parkinson\* NOT (Parkinson\* [AU] OR Wolff-Parkinson))

where the non-drug phrases in CAPS are those used in the Chapter 5 core query, and the lower case phrases are those added for this appendix. There are undoubtedly more non-drug semantic classes that could be added, but we believe the present query provides a good representation of the total core PD non-drug literature.

We entered the query into the PubMed search engine, and retrieved 615 records with Abstracts. The citation for each of the 615 records is as follows:

1: Vafeiadou K, Vauzour D, Spencer JP.  
Neuroinflammation and its modulation by flavonoids.

Endocr Metab Immune Disord Drug Targets. 2007 Sep;7(3):211-24.  
Review.

PMID: 17897048 [PubMed - indexed for MEDLINE]

2: De Cock VC, Lannuzel A, Verhaeghe S, Roze E, Ruberg M, Derenne JP, Willer JC, Vidailhet M, Arnulf I.

REM sleep behavior disorder in patients with guadeloupean parkinsonism, a tauopathy.

Sleep. 2007 Aug 1;30(8):1026-32.

PMID: 17702273 [PubMed - indexed for MEDLINE]

3: Weinreb O, Amit T, Youdim MB.

A novel approach of proteomics and transcriptomics to study the mechanism of

action of the antioxidant-iron chelator green tea polyphenol

(-)-epigallocatechin-3-gallate.

Free Radic Biol Med. 2007 Aug 15;43(4):546-56. Epub 2007 May 16.

PMID: 17640565 [PubMed - indexed for MEDLINE]

4: Balk E, Chung M, Raman G, Tatsioni A, Chew P, Ip S, DeVine D, Lau J.

B vitamins and berries and age-related neurodegenerative disorders.

Evid Rep Technol Assess (Full Rep). 2006 Apr;(134):1-161. Review.

PMID: 17628125 [PubMed - indexed for MEDLINE]

5: Lau FC, Shukitt-Hale B, Joseph JA.

Nutritional intervention in brain aging: reducing the effects of inflammation and

oxidative stress.

Subcell Biochem. 2007;42:299-318. Review.

PMID: 17612057 [PubMed - indexed for MEDLINE]

6: Yadava N, Nicholls DG.

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Broad bean (*Vicia faba*) consumption and Parkinson's disease.  
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Improvement of parkinsonian features correlate with high plasma levodopa  
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New insights on the pathogenesis of neurodegenerative disorders.  
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Pyridine and other coal tar constituents as inhibitors of potato polyphenol oxidase: a non-animal model for neurochemical studies.  
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PMID: 1435072 [PubMed - indexed for MEDLINE]

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Therapy of Morbus Parkinson and radical-induced neurotoxicity in the rat--in vivo voltammetric studies.  
J Neural Transm Suppl. 1992;38:45-53.  
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Long-latency neurodegenerative disease in the western Pacific.

Geriatrics. 1991 Aug;46 Suppl 1:37-42. Review.

PMID: 1894143 [PubMed - indexed for MEDLINE]

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1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity:  
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Neurosci Lett. 1991 Jun 24;127(2):247-50.

PMID: 1881637 [PubMed - indexed for MEDLINE]

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western Pacific region.

Neurology. 1991 May;41(5 Suppl 2):62-6; discussion 66-8. Review.

PMID: 2041595 [PubMed - indexed for MEDLINE]

577: Ramsay RR, Krueger MJ, Youngster SK, Gluck MR, Casida JE, Singer  
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Interaction of 1-methyl-4-phenylpyridinium ion (MPP+) and its analogs  
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rotenone/piericidin binding site of NADH dehydrogenase.

J Neurochem. 1991 Apr;56(4):1184-90.

PMID: 2002336 [PubMed - indexed for MEDLINE]

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Magnesium inhibits the harmful effects on plants of some toxic elements.

Magnes Res. 1991 Mar;4(1):3-7.

PMID: 1863532 [PubMed - indexed for MEDLINE]

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[Parkinson's disease and environmental factors]

Rev Epidemiol Sante Publique. 1991;39(4):373-87. Review. French.

PMID: 1754703 [PubMed - indexed for MEDLINE]

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Transplantation of fetal cells.

Am J Obstet Gynecol. 1991 Jan;164(1 Pt 1):218-30. Review.

PMID: 1670910 [PubMed - indexed for MEDLINE]

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Structure and evolution of a multidomain multiphosphoryl transfer protein. Nucleotide sequence of the fruB(HI) gene in Rhodobacter capsulatus and comparisons with homologous genes from other organisms.

J Mol Biol. 1990 Jun 20;213(4):687-703.

PMID: 2193161 [PubMed - indexed for MEDLINE]

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of amyotrophic lateral sclerosis and parkinsonism-dementia of Guam.

Neurology. 1990 May;40(5):767-72.

PMID: 2330104 [PubMed - indexed for MEDLINE]

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New concepts in the treatment of Parkinson's disease.

Am Fam Physician. 1990 Feb;41(2):574-84. Erratum in: Am Fam Physician 1990

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PMID: 1967895 [PubMed - indexed for MEDLINE]

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Paralysis agitans and levodopa in "Ayurveda": ancient Indian medical treatise.

Mov Disord. 1990;5(1):47-8.

PMID: 2404203 [PubMed - indexed for MEDLINE]

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Parkinson's disease: a case-control study of occupational and environmental risk

factors.

Am J Ind Med. 1990;17(3):349-55.

PMID: 2305814 [PubMed - indexed for MEDLINE]

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Follow-up study of early-life protective and risk factors in Parkinson's disease.

Mov Disord. 1990;5(1):66-70.

PMID: 2296261 [PubMed - indexed for MEDLINE]

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Pharmacokinetics and bioavailability of Sinemet CR: a summary of human studies.

Neurology. 1989 Nov;39(11 Suppl 2):25-38.

PMID: 2685649 [PubMed - indexed for MEDLINE]

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Inhibiting noradrenergic overactivity by inhibition of thromboxane and concomitant activation of opiate receptors via dietary means.

Med Hypotheses. 1989 May;29(1):65-74. Review.

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Tomatoes and Parkinson's disease.

Med Hypotheses. 1989 Feb;28(2):75-9.

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Low-calcium, high-aluminum diet-induced motor neuron pathology in cynomolgus monkeys.

Acta Neuropathol (Berl). 1989;78(2):210-9.

PMID: 2750490 [PubMed - indexed for MEDLINE]

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Epidemiologic study on the association between body burden mercury level and

idiopathic Parkinson's disease.

Neuroepidemiology. 1989;8(3):128-41.

PMID: 2725805 [PubMed - indexed for MEDLINE]

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[Neurologic complications of drug addiction. General aspects.  
Complications  
caused by cannabis, designer drugs and volatile substances]  
Arch Neurobiol (Madr). 1989;52 Suppl 1:143-8. Review. Spanish.  
PMID: 2700291 [PubMed - indexed for MEDLINE]

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A natural and broad spectrum nootropic substance for treatment of SDAT--  
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Ginkgo biloba extract.  
Prog Clin Biol Res. 1989;317:1247-60.  
PMID: 2602410 [PubMed - indexed for MEDLINE]

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Arch Neurol. 1988 Dec;45(12):1350-3.  
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J Neurosci Methods. 1988 Nov;26(1):45-54.  
PMID: 3199847 [PubMed - indexed for MEDLINE]

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Extrapyramidal and other neurologic manifestations associated with carbon  
disulfide fumigant exposure.  
Arch Neurol. 1988 May;45(5):537-40.  
PMID: 2833878 [PubMed - indexed for MEDLINE]

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Interaction of 1-methyl-4-phenylpyridinium ion with human platelets.  
Biochem Biophys Res Commun. 1988 Mar 15;151(2):897-904.  
PMID: 3258155 [PubMed - indexed for MEDLINE]

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Presence of tetrahydroisoquinoline and 1-methyl-tetrahydro-isoquinoline in foods:

compounds related to Parkinson's disease.

Life Sci. 1988;43(4):373-8.

PMID: 3398705 [PubMed - indexed for MEDLINE]

599: Piccardo P, Yanagihara R, Garruto RM, Gibbs CJ Jr, Gajdusek DC.

Histochemical and X-ray microanalytical localization of aluminum in amyotrophic

lateral sclerosis and parkinsonism-dementia of Guam.

Acta Neuropathol (Berl). 1988;77(1):1-4.

PMID: 2467502 [PubMed - indexed for MEDLINE]

600: Yu PH, Boulton AA.

Irreversible inhibition of monoamine oxidase by some components of cigarette smoke.

Life Sci. 1987 Aug 10;41(6):675-82.

PMID: 3613836 [PubMed - indexed for MEDLINE]

601: Steele JC, Guzman T.

Observations about amyotrophic lateral sclerosis and the parkinsonism-dementia

complex of Guam with regard to epidemiology and etiology.

Can J Neurol Sci. 1987 Aug;14(3 Suppl):358-62.

PMID: 3315143 [PubMed - indexed for MEDLINE]

602: Spencer PS.

Guam ALS/parkinsonism-dementia: a long-latency neurotoxic disorder caused by

"slow toxin(s)" in food?

Can J Neurol Sci. 1987 Aug;14(3 Suppl):347-57. Review.

PMID: 3315142 [PubMed - indexed for MEDLINE]

603: Spencer PS, Nunn PB, Hugon J, Ludolph AC, Ross SM, Roy DN, Robertson RC.

Guam amyotrophic lateral sclerosis-parkinsonism-dementia linked to a plant

excitant neurotoxin.

Science. 1987 Jul 31;237(4814):517-22.

PMID: 3603037 [PubMed - indexed for MEDLINE]

604: Perry TL, Hansen S, Jones K.

Exposure to cigarette smoke does not decrease the neurotoxicity of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice.

Neurosci Lett. 1987 Feb 24;74(2):217-20.

PMID: 3494963 [PubMed - indexed for MEDLINE]

605: Baron JA.

Cigarette smoking and Parkinson's disease.

Neurology. 1986 Nov;36(11):1490-6. Review.

PMID: 3531917 [PubMed - indexed for MEDLINE]

606: Ramsay RR, Singer TP.

Energy-dependent uptake of N-methyl-4-phenylpyridinium, the neurotoxic metabolite

of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, by mitochondria.

J Biol Chem. 1986 Jun 15;261(17):7585-7.

PMID: 3486869 [PubMed - indexed for MEDLINE]

607: Peters HA, Levine RL, Matthews CG, Sauter S, Chapman L.

Synergistic neurotoxicity of carbon tetrachloride/carbon disulfide (80/20 fumigants) and other pesticides in grain storage workers.

Acta Pharmacol Toxicol (Copenh). 1986;59 Suppl 7:535-46.

PMID: 3535379 [PubMed - indexed for MEDLINE]

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Behavioural and biochemical changes following chronic administration of L-dopa to

rats.

Eur J Pharmacol. 1982 Apr 23;79(3-4):201-15.

PMID: 7201400 [PubMed - indexed for MEDLINE]

609: Fernstrom JD.

Dietary precursors and brain neurotransmitter formation.

Annu Rev Med. 1981;32:413-25. Review.

PMID: 6111981 [PubMed - indexed for MEDLINE]

610: Manyam NV, Katz L, Hare TA, Gerber JC 3rd, Grossman MH.

Levels of gamma-aminobutyric acid in cerebrospinal fluid in various neurologic disorders.

Arch Neurol. 1980 Jun;37(6):352-5.

PMID: 6446278 [PubMed - indexed for MEDLINE]

611: Seppala T, Linnoila M, Mattila MJ.

Drugs, alcohol and driving.

Drugs. 1979 May;17(5):389-408. Review.

PMID: 37067 [PubMed - indexed for MEDLINE]

612: Elsworth JD, Glover V, Reynolds GP, Sandler M, Lees AJ, Phuapradit P, Shaw

KM, Stern GM, Kumar P.

Deprenyl administration in man: a selective monoamine oxidase B inhibitor without the 'cheese effect'.

Psychopharmacology (Berl). 1978 Apr 14;57(1):33-8.

PMID: 96466 [PubMed - indexed for MEDLINE]

613: Matzkies F.

[Hyperuricemia due to therapeutic measures]

Fortschr Med. 1977 Sep 29;95(36):2195-8. German.

PMID: 914172 [PubMed - indexed for MEDLINE]

614: Leeming RJ, Blair JA, Melikian V, O'Gorman DJ.

Biopterin derivatives in human body fluids and tissues.

J Clin Pathol. 1976 May;29(5):444-51.

PMID: 932231 [PubMed - indexed for MEDLINE]

615: Tate SS, Sweet R, McDowell FH, Meister A.

Decrease of the 3,4-dihydroxyphenylalanine (DOPA) decarboxylase activities in

human erythrocytes and mouse tissues after administration of DOPA.

Proc Natl Acad Sci U S A. 1971 Sep;68(9):2121-3.

PMID: 5289372 [PubMed - indexed for MEDLINE]

## APPENDIX 9 – MULTIPLE SCLEROSIS CORE LITERATURE

This appendix summarizes the MS core literature restricted to select semantic classes. While this is not discovery, since MS is mentioned in each record, nevertheless, there is substantial value in collecting this information in one place. Due to time restrictions, we present article citations only.

The query used to retrieve the MS core literature was restricted to **non-drug** semantic classes, similar conceptually to what was used in Chapter 5. The main difference is that the query used for this appendix contained more non-drug semantic classes than was the case for Chapter 5, but a few less classes than was the case for Appendix 6.. The query used for this appendix may be written as:

(PLANTS, MEDICINAL [MH] OR PLANTS, EDIBLE [MH] OR "PLANT EXTRACTS" [MH] OR "PLANT PREPARATIONS" [MH] OR "PLANT OILS" [MH] OR PHYTOTHERAPY [MH] OR FRUIT [MH] OR VEGETABLES [MH] OR "FISH OILS" [MH] OR ALGAE [MH] OR NUTS [MH] OR "DAIRY PRODUCTS" [MH] OR FATS [MH] OR DIET [MH] OR FLAVONOIDS [MH] OR "DIETARY SUPPLEMENTS" [MH] OR Plants [MH] OR Plankton [MH] OR Plant Components [MH] OR Plant Families and Groups [MH] OR Seedling [MH] OR Trees [MH] OR Algae [MH] OR Algae, Brown [MH] OR Algae, Golden-Brown [MH] OR Algae, Green [MH] OR Algae, Red [MH] OR Lichens [MH] OR Seaweed [MH]) AND (Multiple Sclerosis)

where the non-drug phrases in CAPS are those used in the Chapter 5 core query, and the lower case phrases are those added for this appendix. There are undoubtedly more non-drug semantic classes that could be added, but we believe the present query provides a good representation of the total core MS non-drug literature.

We entered the query into the PubMed search engine, and retrieved 245 records with Abstracts. The citation for each of the 245 records is as follows:

1: Theoharides TC, Kempuraj D, Iliopoulou BP.

Mast cells, T cells, and inhibition by luteolin: implications for the pathogenesis and treatment of multiple sclerosis.



Adv Exp Med Biol. 2007;601:423-30. Review.  
PMID: 17713031 [PubMed - indexed for MEDLINE]

2: Russo EB, Guy GW, Robson PJ.  
Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex,  
a  
cannabis-based medicine.  
Chem Biodivers. 2007 Aug;4(8):1729-43. Review.  
PMID: 17712817 [PubMed - indexed for MEDLINE]

3: Scully C.  
Cannabis; adverse effects from an oromucosal spray.  
Br Dent J. 2007 Sep 22;203(6):E12; discussion 336-7. Epub 2007 Aug 17.  
PMID: 17703180 [PubMed - indexed for MEDLINE]

4: Brahmachari S, Pahan K.  
Sodium benzoate, a food additive and a metabolite of cinnamon, modifies T  
cells  
at multiple steps and inhibits adoptive transfer of experimental allergic  
encephalomyelitis.  
J Immunol. 2007 Jul 1;179(1):275-83.  
PMID: 17579047 [PubMed - indexed for MEDLINE]

5: Sicotte NL, Giesser BS, Tandon V, Klutch R, Steiner B, Drain AE,  
Shattuck DW,  
Hull L, Wang HJ, Elashoff RM, Swerdloff RS, Voskuhl RR.  
Testosterone treatment in multiple sclerosis: a pilot study.  
Arch Neurol. 2007 May;64(5):683-8.  
PMID: 17502467 [PubMed - indexed for MEDLINE]

6: Seamon MJ, Fass JA, Maniscalco-Feichtl M, Abu-Shraie NA.  
Medical marijuana and the developing role of the pharmacist.  
Am J Health Syst Pharm. 2007 May 15;64(10):1037-44. Review.  
PMID: 17494903 [PubMed - indexed for MEDLINE]

7: Ascherio A, Munger KL.  
Environmental risk factors for multiple sclerosis. Part II: Noninfectious  
factors.  
Ann Neurol. 2007 Jun;61(6):504-13. Review.  
PMID: 17492755 [PubMed - indexed for MEDLINE]

8: Lovera J, Bagert B, Smoot K, Morris CD, Frank R, Bogardus K, Wild K, Oken B,

Whitham R, Bourdette D.

Ginkgo biloba for the improvement of cognitive performance in multiple sclerosis:

a randomized, placebo-controlled trial.

Mult Scler. 2007 Apr;13(3):376-85. Epub 2007 Jan 29.

PMID: 17439907 [PubMed - indexed for MEDLINE]

9: Kampman MT, Wilsgaard T, Mellgren SI.

Outdoor activities and diet in childhood and adolescence relate to MS risk above

the Arctic Circle.

J Neurol. 2007 Apr;254(4):471-7. Epub 2007 Mar 21.

PMID: 17377831 [PubMed - indexed for MEDLINE]

10: Fogarty A, Rawstorne P, Prestage G, Crawford J, Grierson J, Kippax S.

Marijuana as therapy for people living with HIV/AIDS: social and health aspects.

AIDS Care. 2007 Feb;19(2):295-301.

PMID: 17364413 [PubMed - indexed for MEDLINE]

11: Collin C, Davies P, Mutiboko IK, Ratcliffe S; Sativex Spasticity in MS Study

Group.

Randomized controlled trial of cannabis-based medicine in spasticity caused by

multiple sclerosis.

Eur J Neurol. 2007 Mar;14(3):290-6.

PMID: 17355549 [PubMed - indexed for MEDLINE]

12: Moser HW, Mahmood A, Raymond GV.

X-linked adrenoleukodystrophy.

Nat Clin Pract Neurol. 2007 Mar;3(3):140-51. Review.

PMID: 17342190 [PubMed - indexed for MEDLINE]

13: Seiwa C, Yamamoto M, Tanaka K, Fukutake M, Ueki T, Takeda S, Sakai R, Ishige

A, Watanabe K, Akita M, Yagi T, Tanaka K, Asou H.

Restoration of FcRgamma/Fyn signaling repairs central nervous system demyelination.

J Neurosci Res. 2007 Apr;85(5):954-66.

PMID: 17290413 [PubMed - indexed for MEDLINE]

14: Mills RJ, Yap L, Young CA.

Treatment for ataxia in multiple sclerosis.

Cochrane Database Syst Rev. 2007 Jan 24;(1):CD005029. Review.

PMID: 17253537 [PubMed - indexed for MEDLINE]

15: Farinotti M, Simi S, Di Pietrantonj C, McDowell N, Brait L, Lupo D, Filippini G.

Dietary interventions for multiple sclerosis.

Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004192. Review.

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PMID: 6746319 [PubMed - indexed for MEDLINE]

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PMID: 6506978 [PubMed - indexed for MEDLINE]

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PMID: 6765305 [PubMed - indexed for MEDLINE]

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PMID: 6278902 [PubMed - indexed for MEDLINE]

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Multiple sclerosis in the Orkney and Shetland Islands. II: The search for an exogenous aetiology.  
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PMID: 7241023 [PubMed - indexed for MEDLINE]

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Arch Neurol. 1980 Jun;37(6):352-5.  
PMID: 6446278 [PubMed - indexed for MEDLINE]

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[Effect of short-term administration of sunflower oil on the blood serum level of linoleic and arachidonic acids and lipids in multiple sclerosis]  
Neurol Neurochir Pol. 1980 Jan-Feb;14(1):27-37. Polish.  
PMID: 7374895 [PubMed - indexed for MEDLINE]

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The nutritional regulation of T lymphocyte function.  
Med Hypotheses. 1979 Sep;5(9):969-85.  
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primrose oil.

Med Hypotheses. 1979 Mar;5(3):365-78.

PMID: 313499 [PubMed - indexed for MEDLINE]

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What if multiple sclerosis isn't an immunological or a viral disease? The case

for a circulating toxin.

Neurochem Res. 1979 Feb;4(1):1-14. Review.

PMID: 377118 [PubMed - indexed for MEDLINE]

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PMID: 88390 [PubMed - indexed for MEDLINE]

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PMID: 707035 [PubMed - indexed for MEDLINE]

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PMID: 884399 [PubMed - indexed for MEDLINE]

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Treatment of detrusor hyperreflexia in multiple sclerosis: a double-blind, crossover clinical trial comparing methantheline bromide (Banthine), flavoxate

chloride (Urispas) and meladrazine tartrate (Lisidonil).

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PMID: 62366 [PubMed - indexed for MEDLINE]

242: Butcher J.

The distribution of multiple sclerosis in relation to the dairy industry and milk consumption.

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PMID: 1067488 [PubMed - indexed for MEDLINE]

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Geochemistry and multiple sclerosis: a hypothesis.

Med J Aust. 1975 Jan 18;1(3):73-7.

PMID: 1128372 [PubMed - indexed for MEDLINE]

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Natural antibodies in human cerebrospinal fluid to rabbit erythrocytes.

Int Arch Allergy Appl Immunol. 1975;49(4):453-63.

PMID: 1171826 [PubMed - indexed for MEDLINE]

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The effect of diet on the fatty acid compositions of serum, brain, brain mitochondria and myelin in the rat.

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PMID: 5881652 [PubMed - indexed for MEDLINE]

## APPENDIX 10 – AMYOTROPHIC LATERAL SCLEROSIS CORE LITERATURE

This appendix summarizes the Amyotrophic Lateral Sclerosis (ALS) core literature restricted to select semantic classes. While this is not discovery, since ALS is mentioned in each record, nevertheless, there is substantial value in collecting this information in one place. Due to time restrictions, we present article citations only.

The query used to retrieve the ALS core literature was restricted to **non-drug** semantic classes, similar conceptually to what was used in Chapter 5. The main difference is that the query used for this appendix contained more non-drug semantic classes than was the case for Chapter 5, but a few less classes than was the case for Appendix 6.. The query used for this appendix may be written as:

(PLANTS, MEDICINAL [MH] OR PLANTS, EDIBLE [MH] OR "PLANT EXTRACTS" [MH] OR "PLANT PREPARATIONS" [MH] OR "PLANT OILS" [MH] OR PHYTOTHERAPY [MH] OR FRUIT [MH] OR VEGETABLES [MH] OR "FISH OILS" [MH] OR ALGAE [MH] OR NUTS [MH] OR "DAIRY PRODUCTS" [MH] OR FATS [MH] OR DIET [MH] OR FLAVONOIDS [MH] OR "DIETARY SUPPLEMENTS" [MH] OR Plants [MH] OR Plankton [MH] OR Plant Components [MH] OR Plant Families and Groups [MH] OR Seedling [MH] OR Trees [MH] OR Algae [MH] OR Algae, Brown [MH] OR Algae, Golden-Brown [MH] OR Algae, Green [MH] OR Algae, Red [MH] OR Lichens [MH] OR Seaweed [MH]) AND (Amyotrophic Lateral Sclerosis)

where the non-drug phrases in CAPS are those used in the Chapter 5 core query, and the lower case phrases are those added for this appendix. There are undoubtedly more non-drug semantic classes that could be added, but we believe the present query provides a good representation of the total core ALS non-drug literature.

We entered the query into the PubMed search engine, and retrieved 104 records with Abstracts. The citation for each of the 104 records is as follows:



- 1: Al-Omar MA.  
The X-linked adrenoleukodystrophy (X-ALD) and oxidative stress.  
J Herb Pharmacother. 2006;6(3-4):125-34. Review.  
PMID: 17317654 [PubMed - indexed for MEDLINE]
  
- 2: Papapetropoulos S.  
Is there a role for naturally occurring cyanobacterial toxins in neurodegeneration? The beta-N-methylamino-L-alanine (BMAA) paradigm.  
Neurochem Int. 2007 Jun;50(7-8):998-1003. Epub 2007 Jan 14. Review.  
PMID: 17296249 [PubMed - indexed for MEDLINE]
  
- 3: Ly PT, Singh S, Shaw CA.  
Novel environmental toxins: steryl glycosides as a potential etiological factor  
for age-related neurodegenerative diseases.  
J Neurosci Res. 2007 Feb 1;85(2):231-7. Review.  
PMID: 17149752 [PubMed - indexed for MEDLINE]
  
- 4: Piquet MA.  
[Nutritional approach for patients with amyotrophic lateral sclerosis]  
Rev Neurol (Paris). 2006 Jun;162 Spec No 2:4S177-4S187. French.  
PMID: 17128108 [PubMed - indexed for MEDLINE]
  
- 5: Fang F, Bellocco R, Hernan MA, Ye W.  
Smoking, snuff dipping and the risk of amyotrophic lateral sclerosis--a prospective cohort study.  
Neuroepidemiology. 2006;27(4):217-21. Epub 2006 Nov 10.  
PMID: 17106211 [PubMed - indexed for MEDLINE]
  
- 6: Xu Z, Chen S, Li X, Luo G, Li L, Le W.  
Neuroprotective effects of (-)-epigallocatechin-3-gallate in a transgenic mouse  
model of amyotrophic lateral sclerosis.  
Neurochem Res. 2006 Oct;31(10):1263-9. Epub 2006 Oct 5.  
PMID: 17021948 [PubMed - indexed for MEDLINE]
  
- 7: Hamadeh MJ, Tarnopolsky MA.  
Transient caloric restriction in early adulthood hastens disease endpoint in male, but not female, Cu/Zn-SOD mutant G93A mice.  
Muscle Nerve. 2006 Dec;34(6):709-19.

PMID: 16941656 [PubMed - indexed for MEDLINE]

8: Galbussera A, Tremolizzo L, Brighina L, Testa D, Lovati R, Ferrarese C, Cavaletti G, Filippini G.

Vitamin E intake and quality of life in amyotrophic lateral sclerosis patients: a follow-up case series study.

Neurol Sci. 2006 Jul;27(3):190-3.

PMID: 16897634 [PubMed - indexed for MEDLINE]

9: Caparros-Lefebvre D, Steele J, Kotake Y, Ohta S.

Geographic isolates of atypical Parkinsonism and tauopathy in the tropics: possible synergy of neurotoxins.

Mov Disord. 2006 Oct;21(10):1769-71.

PMID: 16874753 [PubMed - indexed for MEDLINE]

10: Rao SD, Banack SA, Cox PA, Weiss JH.

BMAA selectively injures motor neurons via AMPA/kainate receptor activation.

Exp Neurol. 2006 Sep;201(1):244-52. Epub 2006 Jun 9.

PMID: 16764863 [PubMed - indexed for MEDLINE]

11: Oyanagi K, Kawakami E, Kikuchi-Horie K, Ohara K, Ogata K, Takahama S, Wada M, Kihira T, Yasui M.

Magnesium deficiency over generations in rats with special references to the pathogenesis of the Parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam.

Neuropathology. 2006 Apr;26(2):115-28.

PMID: 16708544 [PubMed - indexed for MEDLINE]

12: Veldink JH, Kalmijn S, Groeneveld GJ, Wunderink W, Koster A, de Vries JH, van

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Intake of polyunsaturated fatty acids and vitamin E reduces the risk of developing amyotrophic lateral sclerosis.

J Neurol Neurosurg Psychiatry. 2007 Apr;78(4):367-71. Epub 2006 Apr 28.

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Neurodegeneration induced by complex I inhibition in a cellular model of  
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amyotrophic lateral sclerosis.  
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PMID: 16624679 [PubMed - indexed for MEDLINE]

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Thiyagarajan M, Wang J, Pasinetti GM.  
A ketogenic diet as a potential novel therapeutic intervention in  
amyotrophic  
lateral sclerosis.  
BMC Neurosci. 2006 Apr 3;7:29.  
PMID: 16584562 [PubMed - indexed for MEDLINE]

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Cyclin dependent kinase inhibitors prevent apoptosis of postmitotic mouse  
motoneurons.  
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PMID: 16530228 [PubMed - indexed for MEDLINE]

16: Vardeny O, Bromberg MB.  
The use of herbal supplements and alternative therapies by patients with  
amyotrophic lateral sclerosis (ALS).  
J Herb Pharmacother. 2005;5(3):23-31.  
PMID: 16520295 [PubMed - indexed for MEDLINE]

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Cycad toxins, Helicobacter pylori and parkinsonism: cholesterol glucosides  
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common denominator.  
Med Hypotheses. 2006;66(6):1222-6. Epub 2006 Feb 20.  
PMID: 16488551 [PubMed - indexed for MEDLINE]

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Amyotrophic lateral sclerosis in an Italian professional soccer player.  
Parkinsonism Relat Disord. 2006 Jun;12(5):327-9. Epub 2006 Feb 3.  
PMID: 16459125 [PubMed - indexed for MEDLINE]

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Neurodegeneration from mitochondrial insufficiency: nutrients, stem cells, growth factors, and prospects for brain rebuilding using integrative management.  
Altern Med Rev. 2005 Dec;10(4):268-93. Review.  
PMID: 16366737 [PubMed - indexed for MEDLINE]

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The effect of epigallocatechin gallate on suppressing disease progression of ALS model mice.

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Cooler biologically compatible core body temperatures may prolong longevity and combat neurodegenerative disorders.

Med Hypotheses. 2006;66(3):636-42. Epub 2005 Dec 2.  
PMID: 16326025 [PubMed - indexed for MEDLINE]

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Complementary therapy for the treatment of glaucoma: a perspective.  
Ophthalmol Clin North Am. 2005 Dec;18(4):597-609. Review.  
PMID: 16314222 [PubMed - indexed for MEDLINE]

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L, Newhall K, Cudkowicz ME, Brown RH Jr, Bowser R.

Proteomic profiling of cerebrospinal fluid identifies biomarkers for amyotrophic lateral sclerosis.

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Amyotrophic lateral sclerosis: recent advances and future therapies.  
Curr Opin Neurol. 2005 Dec;18(6):712-9. Review.  
PMID: 16280684 [PubMed - indexed for MEDLINE]
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Effect of neuroprotective drugs on gene expression in G93A/SOD1 mice.  
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PMID: 16092101 [PubMed - indexed for MEDLINE]
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Return of the cycad hypothesis - does the amyotrophic lateral  
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Disease-related regressive alterations of forebrain cholinergic system in SOD1

mutant transgenic mice.

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Caloric restriction transiently improves motor performance but hastens clinical

onset of disease in the Cu/Zn-superoxide dismutase mutant G93A mouse.

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Cudkowicz M, Thun MJ.

Vitamin E intake and risk of amyotrophic lateral sclerosis.

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Curr Opin Clin Nutr Metab Care. 2000 Nov;3(6):497-502. Review.

PMID: 11085837 [PubMed - indexed for MEDLINE]

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Population-based case-control study of amyotrophic lateral sclerosis in western

Washington State. II. Diet.

Am J Epidemiol. 2000 Jan 15;151(2):164-73.

PMID: 10645819 [PubMed - indexed for MEDLINE]

64: Trieu VN, Liu R, Liu XP, Uckun FM.

A specific inhibitor of janus kinase-3 increases survival in a transgenic mouse model of amyotrophic lateral sclerosis.  
Biochem Biophys Res Commun. 2000 Jan 7;267(1):22-5.  
PMID: 10623568 [PubMed - indexed for MEDLINE]

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Genistein is neuroprotective in murine models of familial amyotrophic lateral sclerosis and stroke.  
Biochem Biophys Res Commun. 1999 May 19;258(3):685-8.  
PMID: 10329446 [PubMed - indexed for MEDLINE]

66: Esclaire F, Kisby G, Spencer P, Milne J, Lesort M, Hugon J.  
The Guam cycad toxin methylazoxymethanol damages neuronal DNA and modulates tau mRNA expression and excitotoxicity.  
Exp Neurol. 1999 Jan;155(1):11-21.  
PMID: 9918700 [PubMed - indexed for MEDLINE]

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Glutathione peroxidase in amyotrophic lateral sclerosis: the effects of selenium supplementation.  
J Environ Pathol Toxicol Oncol. 1998;17(3-4):325-9.  
PMID: 9726810 [PubMed - indexed for MEDLINE]

68: Oteiza PI, Uchitel OD, Carrasquedo F, Dubrovski AL, Roma JC, Fraga CG.  
Evaluation of antioxidants, protein, and lipid oxidation products in blood from sporadic amyotrophic lateral sclerosis patients.  
Neurochem Res. 1997 Apr;22(4):535-9.  
PMID: 9130267 [PubMed - indexed for MEDLINE]

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Benefit of vitamin E, riluzole, and gabapentin in a transgenic model of familial

amyotrophic lateral sclerosis.

Ann Neurol. 1996 Feb;39(2):147-57.

PMID: 8967745 [PubMed - indexed for MEDLINE]

70: Kasarskis EJ, Berryman S, Vanderleest JG, Schneider AR, McClain CJ.  
Nutritional status of patients with amyotrophic lateral sclerosis: relation to the proximity of death.

Am J Clin Nutr. 1996 Jan;63(1):130-7.

PMID: 8604660 [PubMed - indexed for MEDLINE]

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Individuals with amyotrophic lateral sclerosis are in caloric balance despite losses in mass.

J Neurol Sci. 1995 May;129 Suppl:47-9.

PMID: 7595619 [PubMed - indexed for MEDLINE]

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Screening for non-protein amino acids in seeds of the Guam cycad, *Cycas circinalis*, by an improved GC-MS method.

Planta Med. 1995 Feb;61(1):66-70.

PMID: 7700995 [PubMed - indexed for MEDLINE]

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Nutrition and equine performance.

J Nutr. 1994 Dec;124(12 Suppl):2723S-2729S. Review.

PMID: 7996280 [PubMed - indexed for MEDLINE]

74: Gobe GC.

Apoptosis in brain and gut tissue of mice fed a seed preparation of the cycad *Lepidozamia peroffskyana*.

Biochem Biophys Res Commun. 1994 Nov 30;205(1):327-33.

PMID: 7999044 [PubMed - indexed for MEDLINE]

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Abnormal glycosylation of motor neurons with N-acetyl-D-galactosamine in a case

of subacute motor neuronopathy associated with lymphoma.

J Neurol. 1994 May;241(6):372-5.

PMID: 7931431 [PubMed - indexed for MEDLINE]

76: Moriwaka F, Satoh H, Ejima A, Watanabe C, Tashiro K, Hamada T, Matsumoto A, Shima K, Yanagihara T, Fukazawa T, et al.  
Mercury and selenium contents in amyotrophic lateral sclerosis in Hokkaido, the northernmost island of Japan.  
J Neurol Sci. 1993 Aug;118(1):38-42.  
PMID: 8229049 [PubMed - indexed for MEDLINE]

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Billion-fold difference in the toxic potencies of two excitatory plant amino acids, L-BOAA and L-BMAA: biochemical and morphological studies using mouse brain slices.  
Neurosci Res. 1993 Aug;17(3):241-8.  
PMID: 7901822 [PubMed - indexed for MEDLINE]

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Fasting plasma and CSF amino acid levels in amyotrophic lateral sclerosis: a subtype analysis.  
Acta Neurol Scand. 1993 Jul;88(1):51-5.  
PMID: 8372631 [PubMed - indexed for MEDLINE]

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Neurologic diseases associated with use of plant components with toxic potential.  
Environ Res. 1993 Jul;62(1):106-13. Review.  
PMID: 8325256 [PubMed - indexed for MEDLINE]

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Elevated plasma glucagon in amyotrophic lateral sclerosis.  
Neurology. 1992 Aug;42(8):1532-4.  
PMID: 1641148 [PubMed - indexed for MEDLINE]

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New insights on the pathogenesis of neurodegenerative disorders.  
Acta Neurol (Napoli). 1992 Aug-Dec;14(4-6):455-68. Review.  
PMID: 1338180 [PubMed - indexed for MEDLINE]

- 82: Kisby GE, Ellison M, Spencer PS.  
Content of the neurotoxins cycasin (methylazoxymethanol beta-D-glucoside) and  
BMAA (beta-N-methylamino-L-alanine) in cycad flour prepared by Guam  
Chamorros.  
Neurology. 1992 Jul;42(7):1336-40.  
PMID: 1620343 [PubMed - indexed for MEDLINE]
- 83: Spencer PS, Kisby GE, Ludolph AC.  
Long-latency neurodegenerative disease in the western Pacific.  
Geriatrics. 1991 Aug;46 Suppl 1:37-42. Review.  
PMID: 1894143 [PubMed - indexed for MEDLINE]
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Slow toxins, biologic markers, and long-latency neurodegenerative disease  
in the  
western Pacific region.  
Neurology. 1991 May;41(5 Suppl 2):62-6; discussion 66-8. Review.  
PMID: 2041595 [PubMed - indexed for MEDLINE]
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Amyotrophic lateral sclerosis: fasting plasma levels of cysteine and  
inorganic  
sulfate are normal, as are brain contents of cysteine.  
Neurology. 1991 Apr;41(4):487-90.  
PMID: 2011244 [PubMed - indexed for MEDLINE]
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[Parkinson's disease and environmental factors]  
Rev Epidemiol Sante Publique. 1991;39(4):373-87. Review. French.  
PMID: 1754703 [PubMed - indexed for MEDLINE]
- 87: Duncan MW, Steele JC, Kopin IJ, Markey SP.  
2-Amino-3-(methylamino)-propanoic acid (BMAA) in cycad flour: an  
unlikely cause  
of amyotrophic lateral sclerosis and parkinsonism-dementia of Guam.  
Neurology. 1990 May;40(5):767-72.  
PMID: 2330104 [PubMed - indexed for MEDLINE]
- 88: Sienko DG, Davis JP, Taylor JA, Brooks BR.

Amyotrophic lateral sclerosis. A case-control study following detection of a cluster in a small Wisconsin community.

Arch Neurol. 1990 Jan;47(1):38-41.

PMID: 2294892 [PubMed - indexed for MEDLINE]

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[Determinations of silicon and phosphorus in rice planted in a district of high

incidence of amyotrophic lateral sclerosis by neutron activation and X-ray fluorescence analyses]

Radioisotopes. 1989 Dec;38(12):509-12. Japanese.

PMID: 2616819 [PubMed - indexed for MEDLINE]

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Effects of cyclosporine therapy on plasma lipoprotein levels.

JAMA. 1989 Jul 7;262(1):53-6.

PMID: 2733125 [PubMed - indexed for MEDLINE]

91: Duncan MW, Kopin IJ, Crowley JS, Jones SM, Markey SP.

Quantification of the putative neurotoxin 2-amino-3-(methylamino)propanoic acid

(BMAA) in cycadales: analysis of the seeds of some members of the family Cycadaceae.

J Anal Toxicol. 1989 Jul-Aug;13(4):suppl A-G.

PMID: 2490746 [PubMed - indexed for MEDLINE]

92: Garruto RM, Shankar SK, Yanagihara R, Salazar AM, Amyx HL, Gajdusek DC.

Low-calcium, high-aluminum diet-induced motor neuron pathology in cynomolgus

monkeys.

Acta Neuropathol (Berl). 1989;78(2):210-9.

PMID: 2750490 [PubMed - indexed for MEDLINE]

93: Golbe LI, Farrell TM, Davis PH.

Case-control study of early life dietary factors in Parkinson's disease.

Arch Neurol. 1988 Dec;45(12):1350-3.

PMID: 3196195 [PubMed - indexed for MEDLINE]



- 94: Kisby GE, Roy DN, Spencer PS.  
Determination of beta-N-methylamino-L-alanine (BMAA) in plant (*Cycas circinalis* L.) and animal tissue by precolumn derivatization with 9-fluorenylmethyl chloroformate (FMOC) and reversed-phase high-performance liquid chromatography.  
J Neurosci Methods. 1988 Nov;26(1):45-54.  
PMID: 3199847 [PubMed - indexed for MEDLINE]
- 95: Piccardo P, Yanagihara R, Garruto RM, Gibbs CJ Jr, Gajdusek DC.  
Histochemical and X-ray microanalytical localization of aluminum in amyotrophic lateral sclerosis and parkinsonism-dementia of Guam.  
Acta Neuropathol (Berl). 1988;77(1):1-4.  
PMID: 2467502 [PubMed - indexed for MEDLINE]
- 96: Steele JC, Guzman T.  
Observations about amyotrophic lateral sclerosis and the parkinsonism-dementia complex of Guam with regard to epidemiology and etiology.  
Can J Neurol Sci. 1987 Aug;14(3 Suppl):358-62.  
PMID: 3315143 [PubMed - indexed for MEDLINE]
- 97: Spencer PS.  
Guam ALS/parkinsonism-dementia: a long-latency neurotoxic disorder caused by "slow toxin(s)" in food?  
Can J Neurol Sci. 1987 Aug;14(3 Suppl):347-57. Review.  
PMID: 3315142 [PubMed - indexed for MEDLINE]
- 98: Spencer PS, Nunn PB, Hugon J, Ludolph AC, Ross SM, Roy DN, Robertson RC.  
Guam amyotrophic lateral sclerosis-parkinsonism-dementia linked to a plant excitant neurotoxin.  
Science. 1987 Jul 31;237(4814):517-22.  
PMID: 3603037 [PubMed - indexed for MEDLINE]
- 99: Nunn PB, Seelig M, Zagoren JC, Spencer PS.

Stereospecific acute neuronotoxicity of 'uncommon' plant amino acids linked to human motor-system diseases.  
Brain Res. 1987 May 5;410(2):375-9.  
PMID: 3109690 [PubMed - indexed for MEDLINE]

100: Fujita T.  
Aging and calcium as an environmental factor.  
J Nutr Sci Vitaminol (Tokyo). 1985 Dec;31 Suppl:S15-9.  
PMID: 2943880 [PubMed - indexed for MEDLINE]

101: Slowie LA, Paige MS, Antel JP.  
Nutritional considerations in the management of patients with amyotrophic lateral sclerosis (ALS).  
J Am Diet Assoc. 1983 Jul;83(1):44-7.  
PMID: 6863783 [PubMed - indexed for MEDLINE]

102: Cohn DF, Streifler M.  
Human neurolathyrism, a follow-up study of 200 patients. Part I: Clinical investigation.  
Schweiz Arch Neurol Neurochir Psychiatr. 1981;128(1):151-6.  
PMID: 7244573 [PubMed - indexed for MEDLINE]

103: Syzrantsev IuK, Feoktistov AI.  
[Minimal human requirement for energy and food substances in hypo- and alkinesia]  
Vopr Pitan. 1978 Nov-Dec;(6):18-23. Russian.  
PMID: 726366 [PubMed - indexed for MEDLINE]

104: Felmus MT, Patten BM, Swanke L.  
Antecedent events in amyotrophic lateral sclerosis.  
Neurology. 1976 Feb;26(2):167-72.  
PMID: 946326 [PubMed - indexed for MEDLINE]

## APPENDIX 11 – HUNTINGTON’S DISEASE CORE LITERATURE

This appendix summarizes the Huntington’s Disease (HD) core literature restricted to select semantic classes. While this is not discovery, since HD is mentioned in each record, nevertheless, there is substantial value in collecting this information in one place. Due to time restrictions, we present article citations only.

The query used to retrieve the HD core literature was restricted to **non-drug** semantic classes, similar conceptually to what was used in Chapter 5. The main difference is that the query used for this appendix contained more non-drug semantic classes than was the case for Chapter 5, but a few less classes than was the case for Appendix 6.. The query used for this appendix may be written as:

(PLANTS, MEDICINAL [MH] OR PLANTS, EDIBLE [MH] OR "PLANT EXTRACTS" [MH] OR "PLANT PREPARATIONS" [MH] OR "PLANT OILS" [MH] OR PHYTOTHERAPY [MH] OR FRUIT [MH] OR VEGETABLES [MH] OR "FISH OILS" [MH] OR ALGAE [MH] OR NUTS [MH] OR "DAIRY PRODUCTS" [MH] OR FATS [MH] OR DIET [MH] OR FLAVONOIDS [MH] OR "DIETARY SUPPLEMENTS" [MH] OR Plants [MH] OR Plankton [MH] OR Plant Components [MH] OR Plant Families and Groups [MH] OR Seedling [MH] OR Trees [MH] OR Algae [MH] OR Algae, Brown [MH] OR Algae, Golden-Brown [MH] OR Algae, Green [MH] OR Algae, Red [MH] OR Lichens [MH] OR Seaweed [MH]) AND (Huntington Disease)

where the non-drug phrases in CAPS are those used in the Chapter 5 core query, and the lower case phrases are those added for this appendix. There are undoubtedly more non-drug semantic classes that could be added, but we believe the present query provides a good representation of the total core HD non-drug literature.

We entered the query into the PubMed search engine, and retrieved 43 records with Abstracts. The citation for each of the 43 records is as follows:

- 1: Murck H, Manku M.  
Ethyl-EPA in Huntington disease: potentially relevant mechanism of action.

Brain Res Bull. 2007 Apr 30;72(2-3):159-64. Epub 2006 Nov 15. Review.  
PMID: 17352940 [PubMed - indexed for MEDLINE]

2: Chiang MC, Chen HM, Lee YH, Chang HH, Wu YC, Soong BW, Chen CM, Wu YR, Liu CS, Niu DM, Wu JY, Chen YT, Chern Y.

Dysregulation of C/EBPalpha by mutant Huntingtin causes the urea cycle deficiency

in Huntington's disease.

Hum Mol Genet. 2007 Mar 1;16(5):483-98. Epub 2007 Jan 9.

PMID: 17213233 [PubMed - indexed for MEDLINE]

3: Bogush A, Pedrini S, Pelta-Heller J, Chan T, Yang Q, Mao Z, Sluzas E, Gieringer T, Ehrlich ME.

AKT and CDK5/p35 mediate brain-derived neurotrophic factor induction of DARPP-32

in medium size spiny neurons in vitro.

J Biol Chem. 2007 Mar 9;282(10):7352-9. Epub 2007 Jan 5.

PMID: 17209049 [PubMed - indexed for MEDLINE]

4: McLin JP, Thompson LM, Steward O.

Differential susceptibility to striatal neurodegeneration induced by quinolinic

acid and kainate in inbred, outbred and hybrid mouse strains.

Eur J Neurosci. 2006 Dec;24(11):3134-40.

PMID: 17156374 [PubMed - indexed for MEDLINE]

5: Ayala A, Venero JL, Cano J, Machado A.

Mitochondrial toxins and neurodegenerative diseases.

Front Biosci. 2007 Jan 1;12:986-1007. Review.

PMID: 17127354 [PubMed - indexed for MEDLINE]

6: Ehrnhoefer DE, Duennwald M, Markovic P, Wacker JL, Engemann S, Roark M,

Legleiter J, Marsh JL, Thompson LM, Lindquist S, Muchowski PJ, Wanker EE.

Green tea (-)-epigallocatechin-gallate modulates early events in huntingtin misfolding and reduces toxicity in Huntington's disease models.

Hum Mol Genet. 2006 Sep 15;15(18):2743-51. Epub 2006 Aug 7.

PMID: 16893904 [PubMed - indexed for MEDLINE]

7: Puri BK.

High-resolution magnetic resonance imaging sinc-interpolation-based subvoxel registration and semi-automated quantitative lateral ventricular morphology employing threshold computation and binary image creation in the study of fatty acid interventions in schizophrenia, depression, chronic fatigue syndrome and Huntington's disease.

Int Rev Psychiatry. 2006 Apr;18(2):149-54. Review.

PMID: 16777669 [PubMed - indexed for MEDLINE]

8: Ritch R.

Complementary therapy for the treatment of glaucoma: a perspective.

Ophthalmol Clin North Am. 2005 Dec;18(4):597-609. Review.

PMID: 16314222 [PubMed - indexed for MEDLINE]

9: Van Raamsdonk JM, Pearson J, Rogers DA, Lu G, Barakauskas VE, Barr AM, Honer

WG, Hayden MR, Leavitt BR.

Ethyl-EPA treatment improves motor dysfunction, but not neurodegeneration in the

YAC128 mouse model of Huntington disease.

Exp Neurol. 2005 Dec;196(2):266-72. Epub 2005 Aug 29.

PMID: 16129433 [PubMed - indexed for MEDLINE]

10: Trejo A, Boll MC, Alonso ME, Ochoa A, Velasquez L.

Use of oral nutritional supplements in patients with Huntington's disease.

Nutrition. 2005 Sep;21(9):889-94.

PMID: 16087319 [PubMed - indexed for MEDLINE]

11: Puri BK, Leavitt BR, Hayden MR, Ross CA, Rosenblatt A, Greenamyre JT, Hersch

S, Vaddadi KS, Sword A, Horrobin DF, Manku M, Murck H.

Ethyl-EPA in Huntington disease: a double-blind, randomized, placebo-controlled trial.

Neurology. 2005 Jul 26;65(2):286-92.

PMID: 16043801 [PubMed - indexed for MEDLINE]

- 12: Milakovic T, Johnson GV.  
Mitochondrial respiration and ATP production are significantly impaired in striatal cells expressing mutant huntingtin.  
J Biol Chem. 2005 Sep 2;280(35):30773-82. Epub 2005 Jun 27.  
PMID: 15983033 [PubMed - indexed for MEDLINE]
- 13: Gaba AM, Zhang K, Marder K, Moskowitz CB, Werner P, Boozer CN.  
Energy balance in early-stage Huntington disease.  
Am J Clin Nutr. 2005 Jun;81(6):1335-41.  
PMID: 15941884 [PubMed - indexed for MEDLINE]
- 14: Mattson MP, Duan W, Wan R, Guo Z.  
Prophylactic activation of neuroprotective stress response pathways by dietary and behavioral manipulations.  
NeuroRx. 2004 Jan;1(1):111-6. Review.  
PMID: 15717011 [PubMed - indexed for MEDLINE]
- 15: Qin ZH, Wang J, Gu ZL.  
Development of novel therapies for Huntington's disease: hope and challenge.  
Acta Pharmacol Sin. 2005 Feb;26(2):129-42. Review.  
PMID: 15663888 [PubMed - indexed for MEDLINE]
- 16: Miggiano GA.  
[Strategy for safe nutrition in swallowing disorders]  
Clin Ter. 2004 Apr;155(4):153-7. Italian.  
PMID: 15354765 [PubMed - indexed for MEDLINE]
- 17: Webb JL, Ravikumar B, Rubinsztein DC.  
Microtubule disruption inhibits autophagosome-lysosome fusion: implications for studying the roles of aggresomes in polyglutamine diseases.  
Int J Biochem Cell Biol. 2004 Dec;36(12):2541-50.  
PMID: 15325591 [PubMed - indexed for MEDLINE]
- 18: Derkinderen P, Valjent E, Darcel F, Damier P, Girault JA.  
[Cannabis and cannabinoid receptors: from pathophysiology to therapeutic options]

Rev Neurol (Paris). 2004 Jul;160(6-7):639-49. Review. French.  
PMID: 15247852 [PubMed - indexed for MEDLINE]

19: Miggiano GA.

[Dietetic management of patients with impaired swallowing]  
Clin Ter. 2003 Sep-Oct;154(5):363-8. Italian.  
PMID: 14994927 [PubMed - indexed for MEDLINE]

20: Trejo A, Tarrats RM, Alonso ME, Boll MC, Ochoa A, Velasquez L.  
Assessment of the nutrition status of patients with Huntington's disease.  
Nutrition. 2004 Feb;20(2):192-6.  
PMID: 14962685 [PubMed - indexed for MEDLINE]

21: Verbessem P, Lemiere J, Eijnde BO, Swinnen S, Vanhees L, Van  
Leemputte M,  
Hespeel P, Dom R.  
Creatine supplementation in Huntington's disease: a placebo-controlled pilot  
trial.  
Neurology. 2003 Oct 14;61(7):925-30.  
PMID: 14557561 [PubMed - indexed for MEDLINE]

22: Puri BK, Bydder GM, Counsell SJ, Corridan BJ, Richardson AJ, Hajnal  
JV, Appel  
C, McKee HM, Vaddadi KS, Horrobin DF.  
MRI and neuropsychological improvement in Huntington disease following  
ethyl-EPA  
treatment.  
Neuroreport. 2002 Jan 21;13(1):123-6.  
PMID: 11924873 [PubMed - indexed for MEDLINE]

23: Reiner A, Del Mar N, Meade CA, Yang H, Dragatsis I, Zeitlin S,  
Goldowitz D.  
Neurons lacking huntingtin differentially colonize brain and survive in  
chimeric  
mice.  
J Neurosci. 2001 Oct 1;21(19):7608-19.  
PMID: 11567051 [PubMed - indexed for MEDLINE]

24: Fain JN, Del Mar NA, Meade CA, Reiner A, Goldowitz D.

Abnormalities in the functioning of adipocytes from R6/2 mice that are transgenic for the Huntington's disease mutation.  
Hum Mol Genet. 2001 Jan 15;10(2):145-52.  
PMID: 11152662 [PubMed - indexed for MEDLINE]

25: Naf D, Wilson LA, Bergstrom RA, Smith RS, Goodwin NC, Verkerk A, van Ommen GJ, Ackerman SL, Frankel WN, Schimenti JC.  
Mouse models for the Wolf-Hirschhorn deletion syndrome.  
Hum Mol Genet. 2001 Jan 15;10(2):91-8.  
PMID: 11152656 [PubMed - indexed for MEDLINE]

26: Deckel AW, Volmer P, Weiner R, Gary KA, Covault J, Sasso D, Schmerler N, Watts D, Yan Z, Abeles I.  
Dietary arginine alters time of symptom onset in Huntington's disease transgenic mice.  
Brain Res. 2000 Sep 1;875(1-2):187-95.  
PMID: 10967315 [PubMed - indexed for MEDLINE]

27: Shoham S, Youdim MB.  
Iron involvement in neural damage and microgliosis in models of neurodegenerative diseases.  
Cell Mol Biol (Noisy-le-grand). 2000 Jun;46(4):743-60. Review.  
PMID: 10875437 [PubMed - indexed for MEDLINE]

28: Ferrante RJ, Andreassen OA, Jenkins BG, Dedeoglu A, Kuemmerle S, Kubilus JK, Kaddurah-Daouk R, Hersch SM, Beal MF.  
Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease.  
J Neurosci. 2000 Jun 15;20(12):4389-97.  
PMID: 10844007 [PubMed - indexed for MEDLINE]

29: Muller-Vahl KR, Kolbe H, Schneider U, Emrich HM.  
Cannabis in movement disorders.



Forsch Komplementarmed. 1999 Oct;6 Suppl 3:23-7. Review.  
PMID: 10627163 [PubMed - indexed for MEDLINE]

30: Dragatsis I, Efstratiadis A, Zeitlin S.  
Mouse mutant embryos lacking huntingtin are rescued from lethality by wild-type extraembryonic tissues.  
Development. 1998 Apr;125(8):1529-39.  
PMID: 9502734 [PubMed - indexed for MEDLINE]

31: Zeitlin S, Liu JP, Chapman DL, Papaioannou VE, Efstratiadis A.  
Increased apoptosis and early embryonic lethality in mice nullizygous for the Huntington's disease gene homologue.  
Nat Genet. 1995 Oct;11(2):155-63.  
PMID: 7550343 [PubMed - indexed for MEDLINE]

32: Nasir J, Floresco SB, O'Kusky JR, Diewert VM, Richman JM, Zeisler J, Borowski A, Marth JD, Phillips AG, Hayden MR.  
Targeted disruption of the Huntington's disease gene results in embryonic lethality and behavioral and morphological changes in heterozygotes.  
Cell. 1995 Jun 2;81(5):811-23.  
PMID: 7774020 [PubMed - indexed for MEDLINE]

33: Myers RH, Sax DS, Koroshetz WJ, Mastromauro C, Cupples LA, Kiely DK, Pettengill FK, Bird ED.  
Factors associated with slow progression in Huntington's disease.  
Arch Neurol. 1991 Aug;48(8):800-4.  
PMID: 1832854 [PubMed - indexed for MEDLINE]

34: Morales LM, Estevez J, Suarez H, Villalobos R, Chacin de Bonilla L, Bonilla E.  
Nutritional evaluation of Huntington disease patients.  
Am J Clin Nutr. 1989 Jul;50(1):145-50.  
PMID: 2526577 [PubMed - indexed for MEDLINE]

- 35: Buruma OJ, Van der Kamp W, Barendswaard EC, Roos RA, Kromhout D, Van der Velde EA.  
Which factors influence age at onset and rate of progression in Huntington's disease?  
J Neurol Sci. 1987 Sep;80(2-3):299-306.  
PMID: 2960786 [PubMed - indexed for MEDLINE]
- 36: Farrer LA, Yu PL.  
Anthropometric discrimination among affected, at-risk, and not-at-risk individuals in families with Huntington disease.  
Am J Med Genet. 1985 Jun;21(2):307-16.  
PMID: 3160237 [PubMed - indexed for MEDLINE]
- 37: Sanberg PR, Fibiger HC, Mark RF.  
Body weight and dietary factors in Huntington's disease patients compared with matched controls.  
Med J Aust. 1981 Apr 18;1(8):407-9.  
PMID: 6454826 [PubMed - indexed for MEDLINE]
- 38: Hays SE, Goodwin FK, Paul SM.  
Cholecystokinin receptors in brain: effects of obesity, drug treatment, and lesions.  
Peptides. 1981;2 Suppl 1:21-6.  
PMID: 6267558 [PubMed - indexed for MEDLINE]
- 39: Manyam NV, Katz L, Hare TA, Gerber JC 3rd, Grossman MH.  
Levels of gamma-aminobutyric acid in cerebrospinal fluid in various neurologic disorders.  
Arch Neurol. 1980 Jun;37(6):352-5.  
PMID: 6446278 [PubMed - indexed for MEDLINE]
- 40: Watt JA, Cunningham WL.  
Plasma amino acid levels in Huntington's chorea.  
Br J Psychiatry. 1978 Apr;132:394-7.  
PMID: 147718 [PubMed - indexed for MEDLINE]
- 41: Wurtman RJ, Growdon JH.

Dietary enhancement of CNS neurotransmitters.  
Hosp Pract. 1978 Mar;13(3):71-7.  
PMID: 147851 [PubMed - indexed for MEDLINE]

42: Phillipson OT, Bird ED.  
Plasma glucose, non-esterified fatty acids and amino acids in Huntington's chorea.  
Clin Sci Mol Med. 1977 Mar;52(3):311-8.  
PMID: 139225 [PubMed - indexed for MEDLINE]

43: Phillipson OT, Bird ED.  
Plasma growth hormone concentrations in Huntington's chorea.  
Clin Sci Mol Med. 1976 Jun;50(6):551-4.  
PMID: 132332 [PubMed - indexed for MEDLINE]

## **APPENDIX 12 – WATER PURIFICATION POTENTIAL DISCOVERY CANDIDATES**

Due to the large amount of potential discoveries that were hypothesized by the authors of Chapter 7, not all were able to be fully vetted. Below is a list of all of the potential discovery candidates that have not yet been vetted, but that the authors believe are candidates for potential discovery.

### **12-A. Unvetted Discoveries Obtained Using Clustering-based Literature-based Discovery**

Title: Gill-cleaning mechanisms of *Paratya curvirostris* (Caridea : Atyidae) and comparisons with seven species of Japanese atyid shrimps

Source: JOURNAL OF CRUSTACEAN BIOLOGY

Abstract: Fresh-water atyid shrimps are an ancient group of carideans that uses "passive" cleaning mechanisms to protect their gills from fouling. We studied gill cleaning in *Paratya curvirostris* from New Zealand, and *P. compressa*, *Caridina japonica*, *C. typus*, *C. leucosticta*, *C. serratirostris*, *Neocaridina denticulata*, and *Atyopsis spinipes* from Japan. Gill cleaning in atyids involves epipod-setobranch complexes, associated with their pereopods, and multidenticulate setae on the posterior end of the scaphognathite. Multidenticate scaphognathite setae are particularly well developed in atyids and show a negative correlation with the number of setobranch setae in different species. At one extreme is *A. spinipes*, lacking setobranch setae but having the largest number of multidenticulate scaphognathite setae, which are relatively longer and have the maximum number of digitate scale setules. At the other extreme are *P. curvirostris* and *P. compressa*, with the largest number of setobranch setae but the smallest number of multidenticulate scaphognathite setae, which are relatively shorter and have a smaller number of digitate scale setules. In atyids, there is a compromise between these two gill-cleaning mechanisms. Mapping gill types and gill-cleaning mechanisms on a decapod cladogram suggests that phyllobranchiate gills represent a convergent derived state that evolved independently from trichobranchiate ancestors, in carideans, thalassinids, anomalans, and brachyurans. There are no particular associations between the type of gills and the mechanism used to clean them. "Active" gill cleaning, using pereopods, has evolved independently in several lines. If the primitive gill-cleaning mechanism is setiferous epipods, then epipod-setobranch complexes must have been independently derived in carideans and the astacid-thalassinid group. Multidenticate scaphognathite setae

occur with both setiferous epipods and epipod-setobranch complexes. The multidenticulate scaphognathite setae may be the ancestral state for the Pleocyemata, or a synapomorphy of the Caridea, and the Homarida-Astacida-Thalassinida-Brachyura group, having been lost in the Anomala which have "active"

Discovery Description: The mechanisms of these crustaceans to clean their gills may be applied to membrane filtration technology to prevent/remedy fouling.

Title: Branchiobdellid annelids and their crayfish hosts: are they engaged in a cleaning symbiosis?

Source: OECOLOGIA

Abstract: Branchiobdellid annelids and their freshwater crayfish hosts are generally thought to have a commensal relationship. Branchiobdellids of the genus *Cambarincola* exploit their hosts through a variety of mechanisms; however, an effect of branchiobdellids on crayfish has not been conclusively demonstrated. We investigated whether branchiobdellids positively affect the host crayfish *Cambarus chasmodactylus* in the New River, North Carolina. In a laboratory experiment, we placed 0, 3, or 6 branchiobdellids on *C. chasmodactylus* and observed a significant effect of branchiobdellid presence on both growth and mortality of host crayfish; crayfish with branchiobdellids exhibited faster growth and lower mortality with increasing branchiobdellid density. A tracer experiment demonstrated that branchiobdellids feed on items found in the branchial chamber of *C. chasmodactylus*. We hypothesize that such feeding activity by branchiobdellids reduces fouling of crayfish gills by epibionts and particulate matter and could lead to the reduced mortality and increased growth rates observed in the laboratory experiment. Specifically, *Cambarincola* may improve the ventilatory and excretory fitness of *C. chasmodactylus* by cleaning gill filaments. Field data support this hypothesis by demonstrating that branchiobdellids are found disproportionately at sites proximal to the branchial chamber in the New River. This study provides evidence that the relationship between *C. chasmodactylus* and *Cambarincola* may be a cleaning symbiosis, at least in environments where gill fouling is a problem for *C. chasmodactylus*.

Discovery Description: Branchiobdellid annelids may be used in water purification systems to prevent membrane fouling.

Title: Gill-cleaning mechanisms of the amphibious freshwater crab  
*Geothelphusa dehaani* (Decapoda, Brachyura, Potamidae)

Source: JOURNAL OF CRUSTACEAN BIOLOGY

Abstract: *Geothelphusa dehaani* (White, 1847) is an amphibious crab inhabiting rivers and streams in Japan. Its gill complement consists of nine phyllobranchiate gills, which are cleaned by the passive action of setiferous epipods on all maxillipeds. Epipodal setae are of two types; anchor setae distally have two rows of stout outgrowths with opposing recurved ends (anchor-like), and brush setae have dense needle-like setules distally surrounding the setal shaft. Both setae project from the epipod margins mostly onto gill surfaces, with a few setae inserting between the lamellae. The functional morphology of epipodal grooming in brachyurans is inferred to be a better design solution than in other decapod taxa. Subjecting crabs to dehydration resulted in severe fouling and breakage of epipodal setae, thus indicating the importance of branchial water to gill grooming. Form-function analysis suggested that the use of setiferous epipods as a common gill-cleaning mechanism in the Brachyura was secondarily derived as a result of evolution to a crab-like body form, which caused the tight enclosure of the gills in and the exclusion of the limb bases from the branchial chambers. The epipodal setae, especially anchor setae, of *G. dehaani* were morphologically compared with those of several brachyuran taxa, including other Japanese potamoid species.

Discovery Description: The mechanisms of these crustaceans to clean their gills may be applied to membrane filtration technology to prevent/remedy fouling.

Title: The use of sea urchins to control fouling during suspended culture of bivalves

Source: AQUACULTURE

**Abstract:** We evaluated the efficiency of the sea urchins *Lytechinus variegatus* and *Echinometra lucunter* as a biocontrol of fouling on nets and on bivalve shell of the pearl oyster *Pinctada imbricata* during culture, using suspended pearl nets from long lines, located in Turpialito, Golfo de Cariaco, Venezuela, for 3 months. We established four treatments: nets with (1) two *E. lucunter*, (2) two *L. variegatus*, (3) one *L. variegatus* and one *E. lucunter*, and (4) without sea urchins. At end of the experiment, all sea urchins were alive and the pearl nets with the sea urchins had a significantly less dry mass of net fouling than nets without sea urchins. Although *E. lucunter* reduced the fouling on the nets by 45%, it did not reduced fouling on shells of the oysters. *L. variegatus* reduced fouling on nets by 74% and fouling on the shells by 71%. This work is the first report demonstrating the usefulness of sea urchins in controlling fouling in bivalve culture. We recommend the use of sea urchins to reduce net and shell fouling during the culture of tropical bivalves. (C) 2004 Elsevier B.V. All rights reserved.

**Discovery Description:** Sea urchins may be able to prevent/remedy certain types of fouling in desalination plants.

**Title:** Evidence that a new antibiotic flavone glycoside chemically defends the sea grass *Thalassia testudinum* against zoosporic fungi

**Source:** APPLIED AND ENVIRONMENTAL MICROBIOLOGY

**Abstract:** Significantly fewer thraustochytrid protists (zoosporic fungi) were observed in association with healthy leaf tissue of the marine angiosperm *Thalassia testudinum* than in association with sterilized samples that were returned to the collection site for 48 h. In support of the hypothesis that sea grass secondary metabolites were responsible for these differences, extracts of healthy *T. testudinum* leaf tissues inhibited the growth of the co-occurring thraustochytrid *Schizochytrium aggregatum* and deterred the attachment of *S. aggregatum* motile zoospores to an extract-impregnated substrate. By using *S. aggregatum* for bioassay-guided chemical fractionation, a new flavone glycoside was isolated and structurally characterized as luteolin 7-O-beta-D-glucopyranosyl-2"-sulfate. Whole-leaf tissue concentrations of this metabolite (4 mg/ml of wet leaf tissue) inhibited *S. aggregatum* attachment, and a significantly lower concentration (270  $\mu$ g/ml) reduced thraustochytrid growth by 50%, suggesting that natural concentrations are at least 15 times greater than that needed for significant microbiological

effects. These results offer the first complete chemical characterization of a sea grass sulfated flavone glycoside and provide evidence that a secondary metabolite chemically defends *T. testudinum* against fouling microorganisms.

Discovery Description: This glycoside may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Antibacterial activity of two species of bryozoans from northern Puget Sound

Source: NORTHWEST SCIENCE

Abstract: For the first time, bryozoan species from northern Puget Sound have been shown to contain antibacterial compounds. The antibacterial activity of two local marine cheilostome species was tested against six strains of local marine bacteria and against stock cultures of *Vibrio anguillarum*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli*. The filter paper disc method was used to test for antibacterial activity. A crude extract made from the bryozoan *Bugula pacifica* inhibited the growth of two marine isolates, as well as *B. subtilis*, *S. aureus*, and *E. coli*. A crude extract made from the bryozoan *Tricellaria occidentalis* inhibited the growth of *B. subtilis*. Preliminary scanning electron microscopy data indicate that *Tricellaria occidentalis* had higher densities of surface bacteria than *Bugula pacifica*. This inverse relationship between antibacterial activity and surface fouling may indicate an antifouling role for these bryozoan secondary metabolites. The presence of antibacterial compounds may allow bryozoans to manipulate the microbial film growing on them, and may influence the types of organisms that are able to settle near or on them. The ability to manipulate microbial films may also enable bryozoans to make the substrate nearby more suitable for the settlement of their own larvae.

Discovery Description: The anti-bacterial properties of these bryozoans may be incorporated into membranes or membrane coatings to deter/prevent fouling.



Title: Antimicrobial activity of Caribbean sponge extracts

Source: AQUATIC MICROBIAL ECOLOGY

Abstract: Marine sponges produce a diversity of unusual chemical compounds, but the ecological functions of these metabolites remain largely unknown. To determine if sponge secondary metabolites have ecologically significant antimicrobial effects, organic extracts from 33 species of Caribbean sponges were assayed for antibiotic activity against a test panel of marine bacteria. The test panel consisted of 8 strains representing 6 genera of marine bacteria and included an opportunistic pathogen (*Vibrio parahaemolyticus*), a common fouling bacterium (*Deleya marina*), and strains isolated from seawater and healthy and necrotic Caribbean sponges. Extracts were tested for antibiotic activity at concentrations that were volumetrically equivalent to those found in sponge tissues (whole-tissue concentrations). Bioassay results revealed that 16 species (48 %) exhibited antibiotic activity against at least 1 bacterial isolate and that the 2 bacteria isolated from necrotic sponge tissues were the most sensitive test strains (inhibited by 40 % of the extracts). Extracts from *Amphimedon compressa*, *Amphimedon erina*, *Aplysina lacunosa*, and *Ptilocaulis spiculifera* inhibited the largest numbers of test strains and exhibited the most potent antibiotic activities with values frequently exceeding those of a control antibiotic (gentamicin). The pattern of antimicrobial activity was different for 15 of 16 active sponge species, suggesting that diverse taxa do not produce similar antibacterial metabolites. Overall, only 23 % of the extract/bacterial interactions exhibited antibacterial activity, indicating that, in general, conspicuous members of the Caribbean sponge community do not produce broad-spectrum antibacterial metabolites. All of the species yielding antibacterial extracts also deterred feeding by reef fishes in a previous study, suggesting that some secondary metabolites may have evolved multiple defensive functions. Stevensine, a compound from *Axinella corrugata* (= *Teichaxinella morchella*) known to deter feeding by predatory reef fishes, exhibited weak antimicrobial activity, suggesting that this potent feeding deterrent is not solely responsible for the antimicrobial activity detected in the crude sponge extract.

Discovery Description: The anti-microbial properties of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Antibacterial and repellent activities of marine bacteria associated with algal surfaces

Source: BIOFOULING

Abstract: Despite the ubiquity of bacteria in the marine environment little is known about the structure and function of microbial communities associated with marine macroorganisms. Using a range of traditional and novel culture methods, 280 isolates of epiphytic marine bacteria from a range of marine algae were obtained in pure culture. Sixty of the 280 isolates (21%) exhibited antibiotic activity against a test battery of fouling bacteria.

Fractionation of the culture supernatants derived from two strains, GB3 and AR55, indicated the presence of a multicomponent defense system consisting of both organic and water soluble components. In addition, eight out of 21 strains (38%) screened using a spectrophotometric chemotaxis assay, produced metabolites capable of eliciting a negative chemotactic response in a motile fouling bacterium. A significant fraction of these isolates therefore have the potential to control the microbial population on the seaweed surface, either through inhibiting the growth, or influencing the tactic behavior of potentially competing bacteria.

Discovery Description: The anti-bacterial/repellant properties of these microbial communities may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Chemical defenses against diatom fouling in Antarctic marine sponges

Source: BIOFOULING

Abstract: Antarctic sponges are commonly fouled by diatoms, sometimes so heavily as to occlude pores employed in filter feeding and respiration. This fouling becomes heavier during the annual summer microalgal bloom. Polar and non-polar extracts of eight species of marine sponges from McMurdo Sound, Antarctica were assayed for cytotoxicity against sympatric fouling diatoms. To identify compounds potentially released by sponges as defenses against diatom biofouling, only fractions of crude extracts that were soluble in seawater or 2% methanol in seawater were assayed. Significant bioactivity was present in seven of the eight species. Both *Mycale acerata* and *Homaxinella balfourensis* displayed moderate levels of defense against diatoms even though they are not or are only weakly chemically defended

against bacteria and predators. Calyx acuarii extracts, which do have antipredator and antibacterial effects, had no effect on diatoms except at levels many fold higher than present in the intact animal. These results strongly suggest some level of specificity for chemical defenses against diatom fouling in antarctic sponges.

Discovery Description: The chemical defenses of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Exudation of low molecular weight compounds (thiobismethane, methyl isocyanide, and methyl isothiocyanate) as a possible chemical defense mechanism in the marine sponge *Ircinia felix*

Source: BIOCHEMICAL SYSTEMATICS AND ECOLOGY

Abstract: The volatile constituents of the marine sponge *Ircinia felix* were obtained by dynamic headspace extraction and analyzed by HRGC, HRGC-R IS and HRGC-Odor at sniffing port. Fifty-nine volatiles were identified for the first time in the odor of this sponge. Hydrocarbons (32.9%), alcohols (17.8%) and carbonyl compounds (16.0%) predominated in the sponge volatile profile, followed by esters (11.6%), halogen compounds (8.6%), ethers (7.7%), nitrogen and-or sulfur compounds (4.6%) and carboxylic acids (0.8%). Among the identified volatiles, thiobismethane (commonly known as dimethylsulfide), methyl isocyanide and methyl isothiocyanate were found to be responsible for the nauseating and toxic smell emitted by the sponge and for the antimicrobial activity detected in the volatile extract. Exudation experiments in aquarium and in situ conditions revealed that thiobismethane, methyl isocyanide and methyl isothiocyanate are continuously released by the sponge. Upon injury, the concentration of these volatiles increased strongly. Hence, these substances form a chemical protective barrier which may help these sponges avoid fouling, compete for space, prevent infection in the short term, and/or signal generalist predators regarding the existence of other toxic substances in the internal tissues. (C) 2001 Elsevier Science Ltd. All rights reserved.

Discovery Description: The chemical defenses of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Antagonism of bacterial extracellular metabolites to freshwater-fouling invertebrate zebra mussels, *Dreissena polymorpha*

Source: JOURNAL OF MICROBIOLOGY

Abstract: We investigated the antagonism of indigenous bacteria isolated from stressed mussels and their extracellular metabolites on the adult zebra mussel, *Dreissena polymorpha*. Selective bacterial isolates including *Aeromonas media*, *A. salmonicida*, *A. veronii*, and *Shewanella putrefaciens*, showed strong lethality against adult mussels and 100% mortality was observed within 5 days of incubation. Bacterial metabolites, fractionated and concentrated from stationary-phase culture supernatants of these bacterial isolates, displayed varying degrees of antagonistic effects on zebra mussels. Among the three size fractions examined, <5, 5-10, and > 10 kDa, the most lethal fraction seems to be > 10 kDa for three of the four isolates tested. Further chemical analyses of these size fractions revealed that the predominant constituents were polysaccharides and proteins. No 2-keto-3-deoxyoctanoic acid (2-KDO), deoxyribonucleic acids (DNA) or uronic acid were detectable. Extraction of supernatants of two antagonistic isolates with polar solvent suggested that polar molecules are present in the active fraction. Our data suggest that extracellular metabolites produced by antagonistic bacteria are also involved in disease development in zebra mussels and elucidation of the mechanisms involved may offer a novel strategy for control of biofouling invertebrates.

Discovery Description: The bacterial isolates may be able to deter fouling from zebra mussels and thus be incorporated into water purification systems in which fouling from these organisms is present.

Title: Secondary metabolites as mediators of trophic interactions among antarctic marine organisms

Source: AMERICAN ZOOLOGIST

Abstract: Secondary metabolites are widespread among lower phyla and understanding their functional role(s) in the producing organism has been under study in recent decades. Considerable progress has been made in understanding chemical ecological interactions among terrestrial organisms, and similar research in the marine realm has been initiated in recent years.

Polar regions are more difficult to access and thus progress has been slower. Nevertheless, the extreme and often unique marine environments surrounding Antarctica as well as the many unusual trophic interactions in antarctic marine communities might well be expected to select for novel secondary metabolites and/or novel functional roles for secondary metabolites. Indeed, recent studies have documented novel, chemically-mediated interactions between mollusks and amphipods, between algae, urchins and anemones, and between sponges and their predators. The Porifera are the dominant phylum on the McMurdo Sound benthos, and representatives of this phylum have been shown to elaborate sea star feeding deterrents, inhibitors of fouling or infectious organisms, and metabolites which mediate predation via molt inhibition. As a result of studies on Antarctic sponges, new insights into functional roles of pigments and the ability of sponges to sequester metabolites have been gained, and a new mechanism of chemical defense has been described. Herein we describe recent results of our studies of trophic Interactions between sponges and their predators that are mediated by specific sponge secondary metabolites. Moreover, we highlight unusual chemically-mediated interactions in antarctic marine invertebrates other than sponges.

Discovery Description: The secondary metabolites of these organisms may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Chemical control of bacterial epibiosis and larval settlement of *Hydroides elegans* in the red sponge *Mycale adherens*

Source: BIOFOULING

Abstract: The sponge, *Mycale adherens*, usually occurs within the fouling community of Hong Kong waters, yet its body surface is rarely fouled by other macroorganisms. In this study, sponge-associated bacteria were isolated using enrichment culture techniques and compared with indigenous bacterial isolates from an inanimate reference site in the close vicinity. Bacterial isolates were identified phylogenetically by 16S rRNA gene sequence analysis. The comparison between culturable bacterial communities from the sponge and indigenous benthic bacteria revealed differences both in the total number of isolates and their phylogenetic affiliation. Laboratory bioassays utilizing monospecies bacterial films

revealed that a significant portion of sponge-associated bacteria had either an inhibitory or neutral effect on larval settlement of the fouling polychaete, *Hydroides elegans*. In contrast to natural biofilms, which harbor ca 65% of bacteria with at least some sort of inductive effect on *H. elegans*, statistical analysis showed that only 25% of sponge-associated bacteria were classified as "inductive" strains while the remaining 75% were classified as "non-inductive" strains. Waterborne metabolites of sponges affected the larvae of *H. elegans* in a concentration-dependent manner by either exerting a toxic or an anti-settlement effect. Organic solvent extracts of sponge tissue weakly inhibited growth of bacterial strains isolated from marine biofilms. A potential antifouling mechanism in the sponge *M. adherens* is discussed.

Discovery Description: The chemical defenses of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Bioactive phloroglucinols from the brown alga *Zonaria diesingiana*

Source: JOURNAL OF APPLIED PHYCOLOGY

Abstract: Three phloroglucinols with a C-20 acyl side chain were isolated from marine brown alga *Zonaria diesingiana*. The structures were determined on the basis of NMR spectral analyses and comparison with data in the literature. They all showed antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* and cytotoxic activity by inhibiting cell division in fertilized sea urchin eggs (*Echinometra mathaei*). These activities suggest their possible for pharmacological purposes. These phloroglucinols also showed toxicity against brine shrimp (*Artemia salina*), guppy fish (*Poecilia reticulata*), rice-land shrimp (*Macrobrachium lanchesteri*) and the diatom *Chaetoceros gracilis*. They probably act as chemical defenses against herbivores and also reduce surface fouling by epiphytic algae and larvae, suggesting their important roles in the marine ecosystem.

Discovery Description: The phloroglucinols of this algae may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Localization and ecological significance of oroidin and sceptrin in the Caribbean sponge *Agelas conifera*

Source: BIOCHEMICAL SYSTEMATICS AND ECOLOGY

Abstract: The Caribbean sponge *Agelas conifera* was found to produce a mixture of previously described bromopyrrole alkaloids of which oroidin (1) and sceptrin (2) were predominant. This sponge harbored large populations of heterotrophic bacteria but no photosynthetic symbionts (cyanobacteria). However, 1 and 2 were not associated with the bacteria but with the sponge cells as shown by their distribution in enriched cell fractions obtained by differential centrifugation and Ficoll density gradients. Spherulous cells, found in great abundance in the sponge ectosome, were assumed to be involved in the production of 1 and 2. The target compounds were detected, although in small amounts, in short-term cultures of sponge cells, validating the possibility of a continuous cell culture source. Laboratory assays showed that organic sponge extracts affected the behavior of the coral *Madracis mirabilis* in causing closure and retraction of the polyps at concentrations of the combined compounds 1 and 2 (1:3.3) as low as 0.7 mg/l (0.0125% of the concentration in whole sponges). At higher concentrations (1.4 mg/l) no recovery of the polyps occurred. The extracts, at almost natural concentrations of 1 and 2, deterred feeding by the predatory reef fish *Stegastis partitus*, supporting other reported research. In field experiments, wounding induced a sharp increase of 1 and 2 in the sponge tissues but prolonged predator exclusion by caging and forced confrontation with coral neighbors did not yield measurable changes in 1 and 2 concentrations. All sponges were found to release measurable amounts of bromopyrrole alkaloids in seawater conditioned for 30 min. Crude and fractionated sponge extracts and pure sceptrin (2) were active against bacteria, yeast and filamentous fungi. Taken together, these results support a role of oroidin (1) and sceptrin (2) in defense mechanisms against predators and possibly against space competitors and invading and fouling organisms. (C) 2003 Elsevier Science Ltd. All rights reserved.

Discovery Description: The chemical defenses of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Potential control of bacterial epibiosis on the surface of the sponge *Mycale adhaerens*

Source: AQUATIC MICROBIAL ECOLOGY

Abstract: Terminal restriction fragment length polymorphism (T-RFLP) analysis revealed structural differences in bacterial communities colonizing the surface of the sponge *Mycale adhaerens* or an inanimate reference surface. Since these surfaces are exposed to a common pool of indigenous bacterial colonizers in the water column, the differences in bacterial community structure were attributed to differences in chemical and/or physical characteristics between sponge and reference surfaces. In order to investigate a potential chemical interaction between sponge and bacterial communities, the effect of organic extracts from both the sponge and 20 bacterial isolates from the sponge surface was tested at tissue-level concentration on 36 bacterial isolates from the reference surface. Half of these isolates were susceptible to extract from sponge tissue and 61 % to those of the isolates from the sponge surface; 30 % were sensitive to extracts from both sponge and isolates. In contrast, only 1 of the isolates from the sponge surface was slightly inhibited by the sponge extract (5 %) and none by the extracts from the epibiotic isolates, supporting speculations on potential endo- and exogenous chemical control of bacterial epibiosis by the sponge and epibiotic bacteria, respectively.

Discovery Description: The chemical defenses of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Tenascin-C

Source: INTERNATIONAL JOURNAL OF BIOCHEMISTRY & CELL BIOLOGY

Abstract: Tenascin-C is a hexameric extracellular matrix glycoprotein with multiple isoforms resulting from alternative splicing. Synthesis of tenascin-C occurs in the nervous system, the vasculature and connective tissue components of a number of organs, particularly during development and pathology. Most cells do not express tenascin-C constitutively but expression is induced by growth factors and hormones, such as transforming growth factor-beta and interleukin-1. Tenascin-C is anti-adhesive, but nevertheless is able to influence the differentiation of a variety of cell types. Selective expression of tenascin-C in tumors has led to development of radiolabelled monoclonal anti-tenascin-C antibodies for targeting tumor



therapy, with promising results thus far in clinical trials. (C) 1997 Elsevier Science Ltd.

Discovery Description: Tenascin-C may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Expression of tenascin-C in aseptic loosening of total hip replacement

Source: ANNALS OF THE RHEUMATIC DISEASES

Abstract: Objective - To assess if the bonding interlayer between the implant and bone in aseptic loosening of total hip, replacement (THR) is qualitatively deteriorated by excessive accumulation of anti-adhesive glycoprotein, tenascin-C. Methods - Alkaline phosphatase-antialkaline phosphatase (APAAP) method was used for immunohistochemical staining of tenascin-C in interface tissue and control synovial tissue. Results - Tenascin-C was found to be a major component of the extracellular matrix at a hitherto unrecognized site, namely the synovial membrane-like interface tissue between implant and bone in aseptic loosening of THR. The overall tenascin-C staining (median score 4.0) was greatly increased in aseptic loosening compared with synovial membrane (median score 2.0;  $p < 0.001$ ) and fibrous capsule (median score 2.0;  $p < 0.001$ ) from primary THR operations. Topological analysis disclosed that tenascin-C was also found at the critical implant-interface and interface-bone surfaces. Conclusion - Local tenascin-C expression is increased as a result of a chronic foreign body type reaction associated with excessive cytokine production and tissue injury mediated by microtrauma and neutral endoproteinases. This qualitative and topological deterioration of the bonding interlayer by an increase of anti-adhesive tenascin-C expression may inadvertently contribute to loosening.

Discovery Description: Tenascin-C may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Interference of tenascin-C with syndecan-4 binding to fibronectin blocks cell adhesion and stimulates tumor cell proliferation

Source: CANCER RESEARCH

Abstract: Tenascin-C is an adhesion-modulatory extracellular matrix molecule that is highly expressed in tumors. To investigate the effect of tenascin-C on tumor cells, we analyzed its antiadhesive nature and effect on tumor cell proliferation in a fibronectin context. Glioblastoma and breast carcinoma cell adhesion was compromised by a mixed fibronectin/tenascin-C substratum, which concomitantly caused increased tumor-cell proliferation. We identified the antiadhesive mechanism as a specific interference of tenascin-C with cell binding to the HepII/syndecan-4 site in fibronectin through direct binding of tenascin-C to the 13th fibronectin type III repeat (FNIII13). Cell adhesion and proliferation levels were restored by the addition of FNIII13. Overexpression of syndecan-4, but not syndecan-1 or -2, reverted the cell adhesion defect of tenascin-C. We characterized FNIII13 as the binding site for syndecan-4. Thus we describe a novel mechanism by which tenascin-C impairs the adhesive function of fibronectin through binding to FNIII13, thereby inhibiting the coreceptor function of syndecan-4 in fibronectin-induced integrin signaling.

Discovery Description: Tenascin-C may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Episialin acts as an antiadhesive factor in an in vitro model of human endometrial-blastocyst attachment

Source: BIOLOGY OF REPRODUCTION

Abstract: Episialin, which is found on the apical membrane of human endometrial epithelium, has been postulated to act as an antiadhesive factor through the steric hindrance generated by its extensively glycosylated structure. The present studies were designed to test this hypothesis in an in vitro model of endometrial-blastocyst attachment. Episialin was expressed in human endometrial carcinoma cells (HEC-1A > RL95-2), and attachment of JAr choriocarcinoma cells to the endometrial cell monolayers was inversely related to episialin expression. Treatment of endometrial monolayers with type III sialidase increased JAr binding, and this increase was suppressed by HMFG1, a monoclonal antibody specific for episialin. The effects of sialidase appear to have resulted from a contaminant protease rather than from a loss of sialic acid residues, because sialidase preparations other than type III were ineffective. After sialidase treatment, conditioned

medium from cells treated with type III sialidase contained more episialin than medium from cells treated with other sialidase preparations. Similar attachment-assay results were obtained using O-sialoglycoprotein endopeptidase; after treatment, the increase in JAr binding (>50%) was suppressed by the antiepisialin antibody. These results demonstrate for the first time that episialin acts as an antiadhesive agent in a model of human endometrial-blastocyst attachment.

Discovery Description: Episialin may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Antiadhesive function of 130-kd glycoform of CD43 expressed in CD4 T-lymphocyte clones and transfectant cell lines

Source: BLOOD

Abstract: Conflicting findings regarding proadhesion and antiadhesion in cell-to-cell interactions were previously reported for CD43. We examined possible differences in the role of the 130-kd glycoform and the 115-kd glycoform of CD43 in cellular adhesion in vitro. We generated a monoclonal antibody (MFT3) that discriminates between helper and non-helper murine T-cell clones. Characterization of MFT3 with use of biochemical analysis and complementary DNA (cDNA) transfection experiments showed that it is specific for the 130 kd glycoform of CD43. T-cell clones that expressed the 130-kd CD43 glycoform showed decreased homocytic aggregation and decreased adhesion to spleen cells, B-lymphoma cell lines, and fibroblastic cell lines compared with T-cell clones negative for the 130-kd glycoform. Expression of core 2 beta -1, 6-N-acetylglucosaminyl-transferase (C2GnT) cDNA together with CD43 cDNA resulted in expression of both the 130-kd CD43 glycoform and the 115-kd CD43 glycoform in fibroblastic cell lines. Using these cell lines, we showed that the 130-kd glycoform but not the 115-kd glycoform of CD43 has an antiadhesive function in cellular interactions. Our findings suggest that the antiadhesive function of CD43 is primarily carried out by the 130-kd glycoform. (C) 2000 by The American Society of Hematology.

Discovery Description: The 130-kd glycoform may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: A mechanism for inhibition of E-cadherin-mediated cell-cell adhesion by the membrane-associated mucin episialin MUC1

Source: MOLECULAR BIOLOGY OF THE CELL

Abstract: Episialin (MUC1, PEM, EMA, CA15-3 antigen) is a sialylated, membrane-associated glycoprotein with an extended mucin-like ectodomain. This domain mainly consists of 30-90 homologous 20-amino acid repeats that are rich in O-glycosylation sites (serines and threonines). It is likely that this part forms a polyproline p-turn helix. As a result, the ectodomain can protrude more than 200 nm above the cell surface, whereas most cell surface molecules do not exceed a length of 35 nm. Normally, episialin is present at the apical side of glandular epithelial cells. On carcinoma cells, however, it can be strongly overexpressed and it is often present over the entire cell surface. We have previously shown that episialin, if it is interspersed between adhesion molecules, nonspecifically reduces cell-cell and cell-extracellular matrix interactions in vitro and in vivo, presumably by steric hindrance caused by the extreme length and high density of the episialin molecules at the cell surface. To analyze the molecular mechanism for this anti-adhesion effect in more detail, we have now deleted an increasing number of repeats in the episialin cDNA and transfected the resulting mutants into murine L929 cells expressing the homophilic adhesion molecule E-cadherin. Here we show that the length of episialin is the dominant factor that determines the inhibition of E-cadherin-mediated cell-cell interactions. For the anti-adhesive effect mediated by the full length episialin, charge repulsion by negatively charged sialylated O-linked glycans is far less important.

Discovery Description: The mucin episialin MUC1 may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Mucin and proteoglycan functions in embryo implantation

Source: BIOESSAYS

Abstract: Embryo implantation is a complex series of events that involves changes in pattern of expression of embryonic as well as uterine cell surface components. In the case of the embryo, these changes are driven by the

developmental program. In the case of the uterus, these changes are triggered by both maternal hormonal influences as well as embryo-derived factors. Aspects of the implantation process vary among species; however, interaction between the external surface of the embryonic trophectoderm and the apical surface of the luminal uterine epithelium is a common event. Progress is being made in defining the molecular players in these cell surface interactions. Large-molecular-weight mucin glycoproteins such as MUC1 are present at the apical surface of the uterine epithelium under most conditions. Under most circumstances, these mucins appear to protect the mucosal surface from infection and the action of degradative enzymes. These mucins are antiadhesive and also appear to represent a barrier to embryo attachment. Consistent with this model, reduction of mucin expression is observed in uterine luminal epithelia in many species. Nonetheless, mucin expression persists in the human uterus during the proposed receptive phase. It is possible that mucin loss is localized to implantation sites in humans. Alternatively, mucins may function differently within the context of human implantation than in other species. Studies primarily performed in mice indicate that heparan sulfate proteoglycans, in particular, perlecan, appears on the exterior trophectodermal surface coincident with the acquisition of attachment competence. Various in vitro studies indicate that heparan sulfate proteoglycans support embryo attachment activity that may represent an early event in embryo-uterine interaction. Uterine epithelia cells express several complementary heparan sulfate-binding proteins that may participate in these attachment processes. Use of molecular genetic approaches in mouse models, as well as careful studies of the expression and function of these molecules in the context of implantation in various species, are beginning to shed light on the key molecular events of implantation. (C) 1998 John Wiley & Sons, Inc.

Discovery Description: The mucin MUC1 may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Anti-adhesive property of the plasmin/plasminogen system: the use of plasmin(ogen) for cell detachment and disaggregation in cell culture technique

Source: FIBRINOLYSIS & PROTEOLYSIS

**Abstract:** In recent years, a critical role of the plasmin (Pm) system in remodeling the extracellular matrix and in regulating cell-cell and cell-substratum adhesion has been proposed. In the present study, we provide direct experimental evidence of the anti-adhesive property of the Pm/plasminogen (Pg) system. The addition of Pg or Pm to the cell culture medium (without serum) results in detachment of the cell monolayer from the substrate, either as a sheet or a suspension of cells. It is known that some types of cells produce and secrete plasminogen activators (PAs). The concentration of these proteins on the cell surface was sufficient for Pg activation when Pg was used in our experiments. Cell detachment was observed at a minimal concentration of the inserted Pg or Pm 10-100  $\mu$ g/ml. We have developed a novel cell detachment technique in cell culturing. The procedure is based on the use of Pg (Pm) for cell detachment in cell subcultivation. This technique has some important advantages over the conventional trypsin-based approach. High cell viability and no modifications in cell morphology were observed after Pg(Pm)-induced cell detachment. The rates of cell spreading and monolayer formation increased considerably. The breakage of adhesion contacts did not damage the separated cells. Electron microscopy study of the detached cells indicated that Pm did not have such a destructive effect on the cells as was observed when trypsin was used. Pm from human serum and Pgs from human, bovine, dog or rat sera were used for cell detachment in our experiments. Pgs from the serum of different mammals induced cell detachment differently. The most efficient cell detachment in serum-free medium was induced by dog Pg.

**Discovery Description:** Plasmin or some derivative thereof could be used to create anti-fouling coatings for use on/in filter membranes in water purification systems.

**Title:** Adhesion of macrophages on collagen irradiated with ultraviolet light  
**Source:** JOURNAL OF BIOMATERIALS SCIENCE-POLYMER EDITION

**Abstract:** Properties of collagen irradiated with ultraviolet (UV) light were examined using the techniques of sodium dodecyl sulfate-polyacrylamide gel electrophoresis, spectroscopic measurements, and cell adhesion assay. Both photopolymerization and photodegradation of the collagen appeared to

occur with UV irradiation because the aggregation of collagen and disintegration of the triple-helical structure were observed. The formation of the cross-links between the tyrosine residues in collagen by photoreaction was presumed. The adhesion of macrophages (M phi s) on a polystyrene plate was suppressed by coating the plate surface with collagen. Anti-adhesive activity of collagen on M phi cells decreased with UV irradiation. However, appreciable anti-adhesive activity remained in the modified collagen even when collagen was irradiated with UV light for 24 h.

Discovery Description: Collagen may be used to create anti-fouling membranes or membrane coatings in water purification systems.

Title: INHIBITION OF CELL-ADHESION BY PROTEOLYTIC FRAGMENTS OF TYPE-V COLLAGEN

Source: CELL STRUCTURE AND FUNCTION

Abstract: Type V collagen inhibits the cell-substratum adhesion of many types of cells. In this study, inhibitory effects of type V collagen on the adhesion of mouse melanoma B16-F10 cells to fibronectin, laminin and vitronectin were investigated. When the culture dishes were coated with a mixture of fibronectin and type V collagen, adhesion of the cells was inhibited by 50% at a fibronectin/collagen molar ratio of 10/1. At a similar molar ratio, adhesion of the cells to laminin was inhibited moderately, but that to vitronectin was not significantly affected. Type V collagen added into culture medium was less effective in inhibiting cell adhesion. The antiadhesive activity of type V collagen was partially retained in the alpha1 (V) chain of heat-denatured collagen. The alpha1 (V) chain was split into two large fragments, 90 kDa and 60 kDa, by limited digestion with *Staphylococcus aureus* V8 proteinase. The 90-kDa fragment, which was derived from the C-terminal half of the alpha1 (V) chain, inhibited the cell adhesion more profoundly than alpha1 (V). However, little fibronectin bound to the 90-kDa fragment, while fibronectin bound to the 60-kDa fragment, which was less antiadhesive than the 90-kDa fragment, with the same extent as alpha1 (V). We therefore concluded that the antiadhesive effect of type V collagen was not due to its specific binding to the fibronectin molecule.

Discovery Description: Type V Collagen may be used to create anti-fouling membranes or membrane coatings in water purification systems.

Title: Antiadhesive peptides as the inhibitors of *Mycobacterium kansasii* phagocytosis

Source: PEPTIDES

Abstract: Initial entry of *Mycobacteria* into the cells depends upon the formation of a molecular complex between Antigen 85 (Ag85), located on the bacterial cell wall, and serum protein-fibronectin (FN) [Nat. Struct. Biol. 7 (2000) 141; Nat. Struct. Biol. 7 (2000) 94]. Therefore, a way of preventing a *Mycobacteria* invasion could be to inhibit the interaction between fibronectin and leucocyte cellular receptors of the integrin type. We found that some antiadhesive peptides (such as RGDVY and GRGD), derived of fibronectin and human leucocyte antigen DQ (HLA-DQ) sequences, are in fact very potent inhibitors of *Mycobacterium kansasii* phagocytosis. This observation may open new prospects in the search for tuberculosis therapy. (C) 2003 Elsevier Science Inc. All rights reserved.

Discovery Description: Antiadhesive peptides (such as RGDVY and GRGD), derived of fibronectin and human leucocyte antigen DQ (HLA-DQ) may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Effects of Caribbean sponge secondary metabolites on bacterial surface colonization

Source: AQUATIC MICROBIAL ECOLOGY

Abstract: Crude organic tissue extracts from 8 species of Caribbean sponges were assayed for inhibitory effects on surface colonization using 24 environmental marine bacterial isolates, 4 known marine invertebrate pathogens, and 1 common fouling bacterium. Each extract was tested for its effects on bacterial attachment, growth and swarming. The 24 bacterial strains were isolated from sponge surfaces, nearby substrata, or adjacent seawater. Extracts were incorporated into agar for assays of bacterial attachment and swarming, Growth-inhibition assays were conducted with the standard agar disk-diffusion assay. Of the 24 bacterial isolates, 23 were



significantly inhibited from attaching to an extract-treated agar surface; 1 isolate from the surface of *Agelas conifera* exhibited significantly enhanced attachment on agar treated with the extract of that sponge. Sponge extracts had the least effect on growth: of 184 assays, 11 displayed significant antibacterial activity, all of these from 4 sponge species (*A. conifera*, *Ailochroia crassa*, *Amphimedon compressa*, and *Aplysina fulva*). The same isolate from the surface of *A. conifera* that exhibited enhanced attachment in response to the extract of that sponge exhibited inhibited growth in response to the same extract. Six out of 24 bacterial isolates exhibited swarming, the majority (67%) of which were isolated from substratum sources. Extracts from 4 of the 8 sponge species (the same species as listed above) inhibited swarming in all 6 strains, while the remaining extracts enhanced, inhibited, or had no effect on swarming depending on the strain. Bioassay-guided fractionation of the extract of *A. crassa* yielded 2 compounds responsible for inhibiting attachment and swarming, respectively. Ianthellin was identified as the metabolite that inhibited attachment, whereas another brominated tryosine metabolite inhibited swarming. Chemical defenses of sponges may target microbial attachment, and to a lesser degree influence swarming and growth. Non-toxic metabolites may play the greatest role in affecting bacterial epibiosis on the surfaces of marine sponges.

Discovery Description: The secondary metabolites of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Ecological roles of natural products from the marine sponge *Geodia corticostylifera*

Source: MARINE BIOLOGY

Abstract: In the Brazilian coast, high numbers of the small brittle star *Ophiactis savignyi* usually live associated with the sponge *Geodia corticostylifera* (Demospongiae, Geodidae), but not with other sympatric sponge species. In order to check whether this association was related only with the physical shelter provided by the sponge body or was chemically mediated, the crude organic extract of *G. corticostylifera* was added to sponge mimics made of phytigel and spongin skeleton. Control and treated mimics were simultaneously offered to previously sponge-associated *O. savignyi* in both static seawater and flow-through laboratory experiments. Ophiuroids were allowed to move towards the preferred mimic. The

defensive properties of the sponge extract against fish predation and fouling were also evaluated. Chemotaxis assays showed that symbiotic ophiuroids were able to chemically recognize its host sponge, moving significantly more towards mimics containing *G. corticostylifera* extract. Chemical deterrence assays showed that the natural concentration of the extract of this sponge was also able to inhibit generalist fish predation on field experiments and the attachment of the common mussel *Perna perna* in laboratory assays. These results indicate that the crude extract of *G. corticostylifera* plays multiple functions in the marine environment, presumably being responsible for a closer association of this sponge with *O. savignyi*, providing protection for this ophiuroid and inhibition of epibionts on itself.

Discovery Description: The chemical defenses of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Isolation and characteristic of overlong-chain unsaturated aldehydes from the freshwater sponge *Lubomirskia baicalensis*

Source: RUSSIAN JOURNAL OF BIOORGANIC CHEMISTRY

Abstract: Several unusual overlong-chain unsaturated aldehydes (22 : 1, 22 : 2, 23 : 1, 24 : 1, 24 : 2, and 25 : 2) were found in total lipids of the endemic sponge *Lubomirskia baicalensis* from Baikal Lake. Tetracos-17-enal was identified as the major aldehyde of the mixture using GC-MS and H-1 and C-13 NMR spectroscopy. A procedure for the isolation of total overlong-chain aldehydes was suggested. We think that the overlong-chain aldehydes defend the sponge from fouling and predators.

Discovery Description: The overlong-chain aldehydes of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Antibacterial activities of marine epibiotic bacteria isolated from brown algae of Japan

Source: ANNALS OF MICROBIOLOGY

**Abstract:** One hundred and sixteen epibiotic bacteria were isolated from the surface of nine species of brown algae *Sargassum serratifolium*, *Sargassum fusiforme*, *Sargassum filicinum*, *Padina arborescens*, *Undaria pinnatifida*, *Petalonia fascia*, *Colpomenia sinuosa*, *Scytosiphon lomentaria* and *Ecklonia cava* which were collected at Awaji Island, Japan. Primary screening results using disc-diffusion assay revealed that, among the bacteria isolated 20% of epibiotic bacteria exhibited antibacterial activity. Among them, 10 bacteria which showed high antibacterial activity were further studied for their ability against (i) a set of fouling bacteria isolated from marine natural biofilm, (ii) some luminescent *Vibrio* and *Photobacterium* species and (iii) a panel of pathogenic bacteria. In general, inhibitory activities were high or moderate against fouling bacteria, *Vibrio* and *Photobacterium* species, while they were found to be low against pathogenic bacteria tested. The phylogenetic analysis using 16S rRNA sequencing revealed that all of the bacteria with high antibacterial activity showed a close affiliation with genus *Bacillus*. This result suggested that the genus *Bacillus* is efficient producers of antibacterial compounds and these epibiotic bacteria isolated are highly successful colonizers on macroalgal surfaces.

**Discovery Description:** The antibacterial compounds of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

**Title:** Isolation, structure elucidation, and biological activity of the steroid oligoglycosides and polyhydroxysteroids from the Antarctic starfish *Acodontaster conspicuus*

**Source:** JOURNAL OF NATURAL PRODUCTS

**Abstract:** A total of 19 steroids, of which 13 steroidal oligoglycosides (nine new and four known) and six polyhydroxylated steroids (four new and two known), has been isolated from the Antarctic starfish *Acodontaster conspicuus*. The mixture is dominated by glycosides composed of steroidal aglycons having the hydroxyl groups typically disposed on one side of the tetracyclic nucleus, i.e., 3 beta,4 beta,6 alpha,8,15 beta-, with some having a sulfate at C-6, and differing in the side chains and/or in the disaccharide moieties that are usually attached at C-26, with some at C-28 and C-29. Those compounds are accompanied by minute amounts of glycosides with a Delta(8(14))-double bond in the steroid, which is a structural feature not

previously found among polyhydroxysteroids derived from starfish. Small amounts of six related unglycosidated polyhydroxysteroids and three higher-molecular-weight asterosaponins complete the composition of the mixture. The structures of the new compounds were determined by interpretation of their spectral data and by comparison with spectral data of known compounds. Eighteen of these compounds were evaluated for their ability to inhibit growth in Antarctic marine bacteria isolated from either the water column or the surfaces of benthic marine invertebrates. Of these compounds, 50% were active against at least one Antarctic marine bacterium. This suggests that these compounds may play an important role in deterring microbial fouling.

Discovery Description: The steroid oligoglycosides and polyhydroxysteroids from the Antarctic starfish *Acodontaster conspicuus* may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Methods for reducing biofouling of moored optical sensors

Source: JOURNAL OF ATMOSPHERIC AND OCEANIC TECHNOLOGY

Abstract: Biofouling is one of the primary limiting factors in terms of measurement accuracy and deployment longevity for oceanographic studies involving autonomous sampling. Copper can significantly reduce marine fouling for long-term optical sensor deployments in coastal and open-ocean environments. Copper can effectively replace previously used highly toxic chemical antifoulant methods. Copper-based antifouling systems can be employed with three types of optical sensors: 1) open, 2) enclosed or semienclosed, and 3) shuttered. Copper plates on open-faced backscattering sensors can enable deployment periods of longer than 60 days in coastal waters without biofouling. In addition, copper tubing on nine-wavelength absorption-attenuation meters (ac-9s) has extended measurement capabilities from about 10 days to greater than 60 days with no signs of biofouling in coastal waters. Implementation of copper shutters on optical sensors in open-ocean waters off Japan has resulted in extended deployment periods (410 days and possibly longer) for optical measurements whereas previous optical measurements in the open ocean were typically degraded within several weeks to at most a few months due to biofouling.

Discovery Description: Copper may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Cleaning of concrete fouled by lichens with the aid of Thiobacilli  
Source: MATERIALS AND STRUCTURES

Abstract: Concrete specimens weathered for over a decade in the moderate Belgian climate, showing a black organic outer layer that mainly consisted of lichens, were cleaned with a new biological technique. A mixture of sulphur oxidizing bacteria of the genus *Thiobacillus* supplemented with an appropriate nutrient was applied to a fouled concrete surface, either by sprinkling or by submersion. The aim was to remove the fouled layer in such a way that the surface is uniformly cleaned. The general effect of the technique was evaluated by colorimetry and microscopy. Two sets of weathered concrete specimens, containing blast furnace slag cement or ordinary Portland cement, were investigated. The effectiveness of the technique depended on the cement type of the concrete specimens. The effect on the ordinary portland cement concrete specimens was in some cases up to a factor 2 stronger than the result on the blast furnace slag cement specimens. The sprinkling treatment was about 50% as effective as the submersion treatment but was very promising in the case of in situ acidification. A side effect was the formation of a gypsum layer on some of the specimens, resulting in a whiter color.

Discovery Description: This process or one similar may be used to clean fouled membranes.

Title: Cell fouling resistance of polymer brushes grafted from Ti substrates by surface-initiated polymerization: Effect of ethylene glycol side chain length

Source: BIOMACROMOLECULES 7 (8): 2443-2448 AUG 14 2006

Abstract: This paper presents a comparative study on the antifouling properties of poly(ethylene glycol) (PEG)-based polymer coatings prepared by surface-initiated polymerization (SIP). Three types of poly(oligo(ethylene glycol) methyl ether methacrylate) (POEGMEMA)

polymer thin films of approximate 100 nm thickness were grafted from a catechol initiator that was immobilized on a Ti substrate. OEGMEMA monomers containing side chains of 4, 9, and 23 EG units were used in surface-initiated atom transfer radical polymerization (SI-ATRP) to form POEGMEMA-4, -9, and -23 polymer brushes. The chemical composition, thickness, and wettability of the polymer brushes were characterized by X-ray photoelectron spectroscopy (XPS), ellipsometry, and static water contact angle measurements, respectively. The dependence of antifouling performance on EG side chain length was systemically tested and compared by 3T3 fibroblast cell adhesion assays. Results from 4-h cell culture experiments revealed the complete absence of cell attachment on all the grafted Ti substrates. Excellent cell fouling resistance continued with little dependence on EG side chain length up to three weeks, after which long-term antifouling performance depended on the EG chain length as the grafted samples reached confluent cell coverage in 7, 10, and 11 weeks for POEGMEMA-4, -9, and -23, respectively.

Discovery Description: The antifouling properties of poly(ethylene glycol) (PEG)-based polymer coatings prepared by surface-initiated polymerization (SIP) may be incorporated into water purification membranes to prevent/deter fouling.

Title: Microbial colonization and competition on the marine alga *Ulva australis*

Source: APPLIED AND ENVIRONMENTAL MICROBIOLOGY 72 (8): 5547-5555

Abstract: *Pseudalteromonas tunicata* and *Roseobacter gallaeciensis* are biofilm-forming marine bacteria that are often found in association with the surface of the green alga *Ulva australis*. They are thought to benefit the plant host by producing inhibitory compounds that are active against common fouling organisms. We investigated factors that influence the ability of *P. tunicata* and *R. gallaeciensis* to attach to and colonize the plant surface and also the competitive interactions that occur between these organisms and other isolates from *U. australis* during biofilm formation on the plant surface. A surprisingly high number of *P. tunicata* cells, at least  $10^8$  cells ml<sup>-1</sup>, were required for colonization and establishment of a population of cells that persists on axenic surfaces of *U. australis*. Factors

that enhanced colonization of *P. tunicata* included inoculation in the dark and pregrowth of inocula in medium containing cellobiose as the sole carbon source (cellulose is a major surface polymer of *U. australis*). It was also found that *P. tunicata* requires the presence of a mixed microbial community to colonize effectively. In contrast, *R. gallaeciensis* effectively colonized the plant surface under all conditions tested. Studies of competitive interactions on the plant surface revealed that *P. tunicata* was numerically dominant compared with all other bacterial isolates tested (except *R. gallaeciensis*), and this dominance was linked to production of the antibacterial protein AlpP. Generally, *P. tunicata* was able to coexist with competing strains, and each strain existed as microcolonies in spatially segregated regions of the plant. *R. gallaeciensis* was numerically dominant compared with all strains tested and was able to invade and disperse preestablished biofilms. This study highlighted the fact that microbial colonization of *U. australis* surfaces is a dynamic process and demonstrated the differences in colonization strategies exhibited by the epiphytic bacteria *P. tunicata* and *R. gallaeciensis*.

Discovery Description: The inhibitory compounds produced by *Pseudalteromonas tunicata* and *Roseobacter gallaeciensis* may be incorporated into water purification membranes or membrane coatings to prevent/deter fouling.

Title: Zebra mussel antifouling activity of the marine natural product aaptamine and analogs

Source: MARINE BIOTECHNOLOGY 8 (4): 366-372 JUL-AUG 2006

Abstract: Several aaptamine derivatives were selected as potential zebra mussel (*Dreissena polymorpha*) antifoulants because of the noteworthy absence of fouling observed on *Aaptos* sponges. Sponges of the genus *Aaptos* collected in Manado, Indonesia consistently produce aaptamine-type alkaloids. To date, aaptamine and its derivatives have not been carefully evaluated for their antifoulant properties. Structure-activity relationship studies were conducted using several aaptamine derivatives in a zebra mussel antifouling assay. From these data, three analogs have shown significant antifouling activity against zebra mussel attachment. Aaptamine, iso-aaptamine, and the demethylated aaptamine compounds used in the zebra mussel assay produced EC<sub>50</sub> values of 24.2, 11.6, and 18.6  $\mu$ M, respectively. In addition, neither aaptamine nor iso-aaptamine produced a

phytotoxic response (as high as 300  $\mu$  M) toward a nontarget organism, *Lemna pausicostata*, in a 7-day exposure. The use of these aaptamine derivatives from *Aptos* sp. as potential environmentally benign antifouling alternatives to metal-based paints and preservatives is significant, not only as a possible control of fouling organisms, but also to highlight the ecological importance of these and similar biochemical defenses.

Discovery Description: The antifouling activity of the marine natural product aaptamine produced by *Aptos* sponges could be incorporated into membranes or membrane coatings to inhibit/deter fouling.

Title: Isolation and characterization of some antifouling agents from the brown alga *Sargassum confusum*

Source: JOURNAL OF ASIAN NATURAL PRODUCTS RESEARCH 8 (4): 309-315 JUN 2006

Abstract: Fats and phthalic acid derivatives were isolated and characterized based on their spectral analysis from the antifouling activity guided fractions of n-hexane and methanol extract of the brown alga *Sargassum confusum*. The fractions, as well as the isolated compounds, demonstrated significant antifouling activity against spores of a major fouling alga *Ulva pertusa* with 50-75% decrease of spore attachment on agar-coated slides.

Discovery Description: The antifouling agents of these algae may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Characterization of product capture resin during microbial cultivations

Source: JOURNAL OF INDUSTRIAL MICROBIOLOGY & BIOTECHNOLOGY 33 (6): 445-453 JUN 2006

Abstract: Various bioactive small molecules produced by microbial cultivation are degraded in the culture broth or may repress the formation of additional product. The inclusion of hydrophobic adsorber resin beads to capture these products in situ and remove them from the culture broth can reduce or prevent this degradation and repression. These product capture beads are often subjected to a dynamic and stressful microenvironment for a



long cultivation time, affecting their physical structure and performance. Impact and collision forces can result in the fracturing of these beads into smaller pieces, which are difficult to recover at the end of a cultivation run. Various contaminating compounds may also bind in a non-specific manner to these beads, reducing the binding capacity of the resin for the product of interest (fouling). This study characterizes resin bead binding capacity (to monitor bead fouling), and resin bead volume distributions (to monitor bead fracture) for an XAD-16 adsorber resin used to capture epothilone produced during myxobacterial cultivations. Resin fouling was found to reduce the product binding capacity of the adsorber resin by 25-50%. Additionally, the degree of resin bead fracture was found to be dependent on the cultivation length and the impeller rotation rate. Microbial cultivations and harvesting processes should be designed in such a way to minimize bead fragmentation and fouling during cultivation to maximize the amount of resin and associated product harvested at the end of a run.

Discovery Description: These beads may be introduced into water purification systems such that fouling organisms attach to them instead of the membrane surface, and then the beads and the organisms that foul them can be removed by a screen filtration process.

Title: Less inhibited with age? Larval age modifies responses to natural settlement inhibitors

Source: BIOFOULING 22 (2): 101-106 2006

Abstract: As larvae of marine invertebrates age, their response to settlement cues can change. This change can have significant consequences to both the ecology of these organisms, and to their response to antifouling coatings. This study examines how larval age affects the settlement response of larvae to two naturally derived settlement inhibitors, non-polar extracts from the algae *Delisea pulchra* and *Dilophus marginatus*, the former of which contains compounds that are in commercial development as antifoulants. Two species of marine invertebrates with non-feeding larvae were investigated: the bryozoans *Watersipora subtorquata* and *Bugula neritina*. Larval age strongly affected larval settlement, with older larvae settling at much higher rates than younger larvae. Despite having strong, inhibitory effects on young larvae, the non-polar extracts did not inhibit the settlement of older larvae to the same degree for both species studied. The results show

that the effects of ecologically realistic settlement inhibitors are highly dependent on larval age. Given that the age of settling larvae is likely to be variable in the field, such age specific variation in settlement response of larvae may have important consequences for host-epibiont interactions in natural communities.

Discovery Description: Extracts from these bryozoans could be used to create anti-fouling coatings for membranes or membrane coatings.

Title: An evaluation of the antimicrobial properties of the eggs of 11 species of scleractinian corals

Source: CORAL REEFS 24 (2): 248-253 JUN 2005

Abstract: Potential sources of mortality of marine invertebrate larvae are numerous and include predation and diseases caused by marine microorganisms. Extracts from the eggs of 11 coral species were evaluated for their ability to deter surface attachment and inhibit the growth of two marine tolerant laboratory bacteria and 92 bacterial strains isolated from seawater and the surface of coral colonies on the Great Barrier Reef (GBR). Extracts of the eggs of *Montipora digitata* inhibited the growth of the two laboratory bacteria, *Vibrio harveyi* and *Bacillus subtilis*, and one bacterial isolate from the mucus of the coral *Favia pallida* in disc diffusion and liquid culture assays. No other microbial strains (n=91) from the surface of corals and the reef environment were inhibited by *M. digitata* extracts. No antibacterial activity was found in the egg extracts of the remaining ten coral species and none of the extracts inhibited surface attachment of various bacteria. Extrapolation of estimated surface concentrations of the biologically active extract of *M. digitata* suggests that the level of the growth inhibitory compounds may be sufficient to deter microbial growth in situ.

Discovery Description: Extracts from these scleractinian corals could be used to create anti-fouling coatings for membranes or membrane coatings.

Title: Ecology of Antarctic marine sponges: An overview

Source: INTEGRATIVE AND COMPARATIVE BIOLOGY 45 (2): 359-368 APR 2005

Abstract: Sponges are important components of marine benthic communities of Antarctica. Numbers of species are high, within the lower range for tropical latitudes, similar to those in the Arctic, and comparable or higher than those of temperate marine environments. Many have circumpolar distributions and in some habitats hexactinellids dominate benthic biomass. Antarctic sponge assemblages contribute considerable structural heterogeneity for colonizing epibionts. They also represent a significant source of nutrients to prospective predators, including a suite of spongivorous sea stars whose selective foraging behaviors have important ramifications upon community structure. The highly seasonal plankton blooms that typify the Antarctic continental shelf are paradoxical when considering the planktivorous diets of sponges. Throughout much of the year Antarctic sponges must either exploit alternate sources of nutrition such as dissolved organic carbon or be physiologically adapted to withstand resource constraints. In contrast to predictions that global patterns of predation should select for an inverse correlation between latitude and chemical defenses in marine sponges, such defenses are not uncommon in Antarctic sponges. Some species sequester their defensive metabolites in the outermost layers where they are optimally effective against sea star predation. Secondary metabolites have also been shown to short-circuit molting in sponge-feeding amphipods and prevent fouling by diatoms. Coloration in Antarctic sponges may be the result of relict pigments originally selected for aposematism or UV screens yet conserved because of their defensive properties. This hypothesis is supported by the bioactive properties of pigments examined to date in a suite of common Antarctic sponges.

Discovery Description: The secondary metabolites of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Biochemical composition, energy content and chemical antifeedant and antifoulant defenses of the colonial Antarctic ascidian *Distaplia cylindrica*

Source: MARINE BIOLOGY 145 (5): 885-894 OCT 2004

**Abstract:** The colonial ascidian *Distaplia cylindrica* occurs both as scattered individual colonies or in "gardens" of colonies in fine-grained soft substrata below 20 m depths off Anvers Island along the Antarctic Peninsula. Individual colonies, shaped as tall rod-like cylinders and anchored in the sediments by a bulbous base, may measure up to 7 m in height. *D. cylindrica* represent a considerable source of materials and energy for prospective predators, as well as potential surface area for fouling organisms. Nonetheless, qualitative in situ observations provided no evidence of predation by sympatric predators such as abundant sea stars, nor obvious biofouling of colony surfaces. Mean energy content of whole-colony tissue of *D. cylindrica* was relatively high for an ascidian (14.7 kJ g(-1) dry wt), with most of this energy attributable to protein (12.7 kJ g(-1) dry wt). The sympatric omnivorous sea star *Odontaster validus* consistently rejected pieces of *D. cylindrica* colonies in laboratory feeding assays, while readily ingesting similarly sized alginate food pellets. Feeding deterrence was determined to be attributable to defensive chemistry, as colonies of *D. cylindrica* are nutritionally attractive and lack physical protection (conspicuous skeletal elements or a tough outer tunic), and *O. validus* display significant feeding-deterrent responses to alginate food pellets containing tissue-level concentrations of organic extracts. In addition, high acidity measured on outer colony surfaces (pH 1.5) as well as homogenized whole-colony tissues (pH 2.5) are indicative of surface sequestration of inorganic acids. Agar food pellets prepared at tissue levels of acidity resulted in significant feeding deterrence in sea stars. Thus, both inorganic acids and secondary metabolites contribute to chemical feeding defenses. *D. cylindrica* also possesses potent antifoulant secondary metabolites. Tissue-level concentrations of hydrophilic and lipophilic extracts caused significant mortality in a sympatric pennate diatom. Chemical feeding deterrents and antifoulants are likely to contribute to the abundance of *D. cylindrica* and, in turn, play a role in regulating energy transfer and community structure in benthic marine environments surrounding Antarctica.

**Discovery Description:** The chemical feeding deterrents and antifoulants produced by colonial ascidian *Distaplia cylindrica* may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Chemical defense and antifouling activity of three Mediterranean sponges of the genus *Ircinia*

Source: ZEITSCHRIFT FUR NATURFORSCHUNG C-A JOURNAL OF BIOSCIENCES 57 (1-2): 161-171 JAN-FEB 2002

Abstract: The defense roles and the antifouling activity of the organic extracts and the major metabolites of the sponges *Ircinia oros*, *I. variabilis* and *I. spinosula* were investigated. The antifeedant activity was tested in experimental aquaria on the generalist predator fish *Thalassoma pavo* as well as in coastal ecosystems rich in fishes. Some of the major metabolites exhibited high levels of antifeedant activity. The antifouling activity was tested in laboratory assays, against representatives of the major groups of fouling organisms (marine bacteria, marine fungi, diatoms, macroalgae and mussels). All extracts showed promising levels of activity. As was expected, no single extract was active in all tests and some fractions that were effective against one organism showed little or no activity against the others. The high but variable level of antifouling activity in combination with the absence of toxicity (tested on the development of oyster and sea urchin larvae) shows the potential of these metabolites to become ingredients in environmentally friendly antifouling preparations.

Discovery Description: The chemical defenses of these sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Antifouling activities expressed by marine surface associated *Pseudoalteromonas* species

Source: FEMS MICROBIOLOGY ECOLOGY

Abstract: Members of the marine bacterial genus *Pseudoalteromonas* have been found in association with living surfaces and are suggested to produce bioactive compounds against settlement of algal spores, invertebrate larvae, bacteria and fungi. To determine the extent by which these antifouling activities kind the production of bioactive compounds are distributed amongst the members of the genus *Pseudoalteromonas*, 10 different *Pseudoalteromonas* species mostly derived from different host organisms were tested in a broad range of biofouling bioassays. These assays included the settlement of larvae of two ubiquitous invertebrates *Hydroides elegans* and *Balanus amphitrite* as well as the settlement of spores of the common fouling algae *Ulva lactuca* and *Polysiphonia* sp. The growth of bacteria and

fungi, which are the initial fouling organisms on marine surfaces, was also assayed in the presence of each of the 10 *Pseudoalteromonas* species. It was found that most members of this genus produced a variety of bioactive compounds. The broadest range of inhibitory activities was expressed by *Pseudoalteromonas tunicata* which inhibited all target fouling organisms. Only two species, *Pseudoalteromonas haloplanktis* and *Pseudoalteromonas nigrifaciens*, displayed negligible activity in the bioassays. These were also the only two nonpigmented species tested in this study which indicates a correlation between production of bioactive compounds and expression of pigment. Three members, *P. tunicata*, *Pseudoalteromonas citrea* and *Pseudoalteromonas rubra*, were demonstrated to express autoinhibitory activity. It is suggested that most *Pseudoalteromonas* species are efficient producers of antifouling agents and that the production of inhibitory compounds by surface associated *Pseudoalteromonas* species may aid the host against colonization of its surface. (C) 2002 Federation of European Microbiological Societies. .Published by Elsevier Science B.V. All rights reserved.

Discovery Description: The bioactive compounds produced by the marine bacterial genus *Pseudoalteromonas* may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: The photoresponse of a molybdenum porphyrin makes an artificial gill feasible

Source: JOURNAL OF MEMBRANE SCIENCE 249 (1-2): 235-243 MAR 1 2005

Abstract: An artificial gill has been developed that transfers oxygen from water to air, using oxo-molybdenum(IV)5,10,15,20-tetramesitylporphyrin ((MoO)-O-IV(tmp)) dissolved in o-xylene as an oxygen carrier solution and the energy of visible light. The oxygen partial pressure in the oxygen carrier solution is changed by photo-irradiation to enhance both the oxygen uptake from water and the oxygen release to air. The ratio of the oxygen mass transfer coefficient of the oxygen carrier solution to that of water is 0.746 for oxygen uptake and 0.654 for oxygen release. In designing a large-scale artificial gill for supplying oxygen to a closed space underwater such as submerged vessel, the required membrane surface area, the seawater flow rate and the reservoir tank volume were 123 m<sup>2</sup>, 0.00533 m<sup>3</sup> s<sup>-1</sup>, and

5.06 m(3), respectively. These values increased as the oxygen partial pressure of seawater decreased. However, the high partial pressure of oxygen required for human respiration (20.0 kPa) can be provided in a closed space even from seawater with an oxygen partial pressure as low as 10.0 kPa. This newly developed artificial gill may be useful for deep sea activities, such as underwater exploration, marine research and underwater habitation. (C) 2004 Elsevier B.V. All rights reserved.

Discovery Description: An artificial gill may be modified so that it filters water, or removes oxygen from the water thus neutralizing any aerobic bacteria.

Title: c-di-GMP (3'-5'-cyclic diguanylic acid) inhibits *Staphylococcus aureus* cell-cell interactions and biofilm formation.

Source: Curr Microbiol. 2005 Mar;50(3):145-50. Epub 2005 Mar 15.

Abstract: *Staphylococcus aureus* is an important pathogen of humans and animals, and antibiotic resistance is a public health concern. Biofilm formation is essential in virulence and pathogenesis, and the ability to resist antibiotic treatment results in difficult-to-treat and persistent infections. As such, novel antimicrobial approaches are of great interest to the scientific, medical, and agriculture communities. We recently proposed that modulating levels of the cyclic dinucleotide signaling molecule, c-di-GMP (cyclic diguanylate [3',5'-cyclic diguanylic acid], cGpGp), has utility in regulating phenotypes of prokaryotes. We report that extracellular c-di-GMP shows activity against human clinical and bovine intramammary mastitis isolates of *S. aureus*, including methicillin-resistant *S. aureus* (MRSA) isolates. We show that chemically synthesized c-di-GMP is soluble and stable in water and physiological saline and stable following boiling and exposure to acid and alkali. Treatment of *S. aureus* with extracellular c-di-GMP inhibited cell-to-cell (intercellular) adhesive interactions in liquid medium and reduced (>50%) biofilm formation in human and bovine isolates compared to untreated controls. c-di-GMP inhibited the adherence of *S. aureus* to human epithelial HeLa cells. The cyclic nucleotide analogs cyclic GMP and cyclic AMP had a lesser inhibitory effect on biofilms, while 5'-GMP had no major effect. We propose that cyclic dinucleotides such as c-di-GMP, used either alone or in combination with other antimicrobial agents, represent a novel and attractive

approach in the development of intervention strategies for the prevention of biofilms and the control and treatment of infection.

Discovery Description: Cyclic dinucleotides such as c-di-GMP may be used to prevent biofilms or may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Removing selenite from groundwater with an in situ biobarrier: laboratory studies.

Source: Environ Sci Technol. 2005 Apr 1;39(7):2327-33.

Abstract: Laboratory biobarriers were evaluated for their ability to remove selenite from flowing groundwater. Microbial activity in aquifers is usually limited by substrate availability, and biobarriers stimulate microbial activity by providing a substrate; for these studies soybean oil was used. Water containing 10 mg L<sup>-1</sup> selenite-Se was pumped through the biobarriers for 74 days and the amount present in the effluent monitored. The amounts remained high for the first 2 weeks of the study but then declined. From day 28 until the end of the study the amount of selenite-Se in the column effluents averaged 0.20 +/- 0.04 mg L<sup>-1</sup>, a decrease of approximately 98%. At the end of the study about half of the selenite-Se applied to the columns was recovered as immobilized selenium trapped by the biobarrier. This study suggests that biobarriers containing vegetable oil might be used as a process for removing selenite from contaminated groundwater.

Discovery Description: Biobarriers may be used as a novel method to filter water in water purification plants.

Title: Multi objective optimization of the setup of a surfactant-enhanced DNAPL remediation.

Source: J Agric Food Chem. 2005 Jun 15;53(12):4906-10

Abstract: Surfactant-enhanced aquifer remediation (SEAR) is widely considered a promising technique to remediate dense nonaqueous phase liquid (DNAPL) contaminations in-situ. The costs of a SEAR remediation are important and depend mostly on the setup of the remediation. Costs can



be associated with the installation of injection and extraction wells, the required time of the remediation (and thus labor costs, lease of installations, and energy), the extracted water volume (the purification of the extracted water), and the injected surfactant amount. A cost-effective design of the remediation setup allows an optimal use of resources. In this work, a SEAR remediation was simulated for a hypothetical typical DNAPL contamination. A constrained multi-objective optimization of the model was applied to obtain a Pareto set of optimal remediation strategies with different weights for the two objectives of the remediation: (i) the maximal removal of DNAPL mass (ii) with a minimal total cost. A relatively sharp Pareto front was found, showing a considerable tradeoff between DNAPL removal and total remediation costs. These Pareto curves can help decision makers select an optimal remediation strategy in terms of cost and remediation efficiency depending on external constraints such as the available budget and obligatory remediation goals.

Discovery Description: The techniques of SEAR may be incorporated into traditional water purification plants for possible cost savings.

Title: 2 - 5,5-Dimethyl-2-pyrrolidone-N-oxyl Formation in Electron Spin Resonance Studies of Electrolyzed NaCl Solution Using 5,5-Dimethyl-1-pyrroline-N-oxide as a Spin Trapping Agent.

Source: Trends Biotechnol. 2005 May 25; [Epub ahead of print]

Abstract: Electrolyzed oxidizing (EO) water has recently generated much interest as a disinfectant in the food industry. 5,5-Dimethyl-1-pyrroline-N-oxide (DMPO) is a spin trapping agent widely used in the electron spin resonance (ESR) characterization of oxygen-centered free radicals. The reaction between electrolyzed water, collected from the anode side of a two-chamber electrolyzer, and DMPO was investigated by ESR spectroscopy. Addition of DMPO to EO water generated an ESR spectrum identical to that of 5,5-dimethyl-2-pyrrolidone-N-oxyl (DMPOX), suggesting that a compound from EO water oxidized DMPO with the formation of DMPOX. To further investigate the electrolytically generated compound that oxidized DMPO, aqueous solutions of different sodium salts (sodium chloride, sodium citrate, and sodium iodide) with similar conductivities were electrolyzed. The DMPOX signal was not detected in the electrolyzed sodium citrate sample, suggesting that DMPOX formation in the

electrolyzed NaCl sample might be due to an electrolytically generated chlorine species. A low DMPOX signal was also observed from the electrolyzed NaI sample, suggesting that a similar species obtained through the electrolysis of I(-) can also oxidize DMPO. Hypochlorous acid is proposed to oxidize the spin trap DMPO with the formation of DMPOX. In a neutral pH environment, electrolyzed water also oxidized DMPO to DMPOX. This is consistent with the DMPOX formation in the reaction of chlorine water (containing HOCl and Cl(2)) or sodium hypochlorite with DMPO.

Discovery Description: Electrolyzed oxidizing (EO) water could be used to disinfect water instead of/ in conjunction with traditional techniques.

Title: Uranium removal from aqueous solution by coir pith: equilibrium and kinetic studies.

Source:

Abstract: Basic aspects of uranium adsorption by coir pith have been investigated by batch equilibration. The influence of different experimental parameters such as final solution pH, adsorbent dosage, sorption time, temperature and various concentrations of uranium on uptake were evaluated. Maximum uranium adsorption was observed in the pH range 4.0-6.0. The Freundlich and Langmuir adsorption models were used for the mathematical description of the adsorption equilibrium. The equilibrium data fitted well to both the equilibrium models in the studied concentration range of uranium (200-800 mg/l) and temperatures (305-336 K). The coir pith exhibited the highest uptake capacity for uranium at 317 K, at the final solution pH value of 4.3 and at the initial uranium concentration of 800 mg/l. The kinetics of the adsorption process followed a second-order adsorption. The adsorbent used proved to be suitable for removal of uranium from aqueous solutions. 0.2 N HCl was effective in uranium desorption. The results indicated that the naturally abundant coir pith of otherwise nuisance value exhibited considerable potential for application in removal of uranium from aqueous solution.

Discovery Description: Coir pith may be used to remove contaminants from water.

Title: Osmosis and solute-solvent drag - Fluid transport and fluid exchange in animals and plants

Source: CELL BIOCHEMISTRY AND BIOPHYSICS 42 (3): 277-345 2005

Abstract: In 1903, George Hulett explained how solute alters water in an aqueous solution to lower the vapor pressure of its water. Hulett also explained how the same altered water causes osmosis and osmotic pressure when the solution is separated from liquid water by a membrane permeable to the water only. Hulett recognized that the solute molecules diffuse toward all boundaries of the solution containing the solute. Solute diffusion is stopped at all boundaries, at an open-unopposed surface of the solution, at a semipermeable membrane, at a container wall, or at the boundary of a solid or gaseous inclusion surrounded by solution but not dissolved in it. At each boundary of the solution, the solute molecules are reflected, they change momentum, and the change of momentum of all reflected molecules is a pressure, a solute pressure (i.e., a force on a unit area of reflecting boundary). When a boundary of the solution is open and unopposed, the solute pressure alters the internal tension in the force bonding the water in its liquid phase, namely, the hydrogen bond. All altered properties of the water in the solution are explained by the altered internal tension of the water in the solution. We acclaim Hulett's explanation of osmosis, osmotic pressure, and lowering of the vapor pressure of water in an aqueous solution. His explanation is self-evident. It is the necessary, sufficient, and inescapable explanation of all altered properties of the water in the solution relative to the same property of pure liquid water at the same externally applied pressure and the same temperature. We extend Hulett's explanation of osmosis to include the osmotic effects of solute diffusing through solvent and dragging on the solvent through which it diffuses. Therein lies the explanations of (1) the extravasation from and return of interstitial fluid to capillaries, (2) the return of luminal fluid in the proximal and distal convoluted tubules of a kidney nephron to their peritubular capillaries, (3) the return of interstitial fluid to the vasa recta, (4) return of aqueous humor to the episcleral veins, and (5) flow of phloem from source to sink in higher plants and many more examples of fluid transport and fluid exchange in animal and plant physiology. When a membrane is permeable to water only and when it separates differing aqueous solutions, the flow of water is from the solution with the lower osmotic pressure to the solution with the higher osmotic pressure. On the contrary, when no diffusion barrier separates differing parts of an aqueous solution, fluid may flow from the part with the

higher osmotic pressure to the part with the lower osmotic pressure because the solute molecules diffuse toward their lower concentration and they drag on the water through which they diffuse. This latter osmotic effect (diffusing solute dragging on solvent or counter osmosis) between differing parts of a solution has long been neglected and ignored when explaining fluid fluxes in plant and animal physiology. For two solutions separated by a semipermeable membrane, osmosis is the flow of its solvent from the solution with the lower solute concentration into the solution with the higher Solute concentration. For two contiguous solutions not separated by a semipermeable membrane, counter osmosis is the flow of solution with the higher solute concentration toward the Solution with the lower solute concentration. Corrective treatment of medical disorders attributable to faulty distribution of body fluids (e.g. , glaucoma, pulmonary edema, systemic edema) are possible with these new insights regarding fluid transport and exchange provided in this review.

Discovery Description: The principles behind fluid transport and fluid exchange in animals and plants could be utilized to redesign existing water purification methodologies and techniques.

Title: Characteristics of natural organic matter degradation in water by UV/H<sub>2</sub>O<sub>2</sub> treatment

Source: ENVIRONMENTAL TECHNOLOGY 27 (3): 277-287 MAR 2006

Abstract: This study evaluated the UV/H<sub>2</sub>O<sub>2</sub> system for degradation of natural organic matter in water. The photolysis experiments were conducted in a 10-1 batch reactor using a 450-watt high-pressure mercury vapor lamp as the light source. The addition of H<sub>2</sub>O<sub>2</sub> in water greatly improved the rate of humic acid degradation by UV light and 90% of the humic acid was removed within 30 min of photolysis. Kinetic data showed that the first-order reaction could be used to describe the kinetics of both humic acid oxidation and H<sub>2</sub>O<sub>2</sub> decomposition, and the optimum H<sub>2</sub>O<sub>2</sub> dose was 0.01% similar to 0.05% for humic acid oxidation. It was also observed that the absorption of UVC (UV with wavelength between 200 and 280 nm) is responsible for the dissociation of H<sub>2</sub>O<sub>2</sub> to generate the reactive hydroxyl radicals. Depending on the initial dosages, the H<sub>2</sub>O<sub>2</sub> added to the system can be completely decomposed by UV within 50 to 90 minutes. Upon UV irradiation, the humic intermediates with smaller molecular sizes increase as

a result of the degradation of larger humic substances. Photolysis of surface water also shows that the UV/H<sub>2</sub>O<sub>2</sub> was effective in reducing trihalomethanes (THMs) formation in treating surface water with high contents of organic precursors. The distribution of THMs shifted from chlorine-THMs to bromine-THMs after UV/H<sub>2</sub>O<sub>2</sub> treatments when bromide was present in water. However, higher H<sub>2</sub>O<sub>2</sub> dosages would be necessary for the photolysis of surface water containing high concentrations of organic THM precursors. As observed from the Fourier transform infrared (FTIR) spectra, the functional groups of treated humic acids were destructed significantly, including -OH (from -COOH and -COH), aromatic -C=C, and -C=O conjugated with aromatic rings.

Discovery Description: UV/H<sub>2</sub>O<sub>2</sub> treatment could be used to degrade NOM.

Title: Microbial communities in wetlands of the Athabasca oil sands: genetic and metabolic characterization

Source: FEMS MICROBIOLOGY ECOLOGY 55 (1): 68-78 JAN 2006

Abstract: Naphthenic acids are a complex family of naturally occurring cyclic and acyclic carboxylic acids that are present in the acidic fraction of petroleum. Naphthenic acids are acutely toxic to aquatic organisms. Previous studies showed that wetland sediments exposed to oil sands process water containing naphthenic acids had higher rates of naphthenic acid degradation in vitro compared with unexposed wetlands. In this study we compare the microbial community structures in sediments from wetlands exposed to different amounts of oil sands process water using BIOLOG, phospholipid fatty acid analysis and denaturing gradient gel electrophoresis of total bacterial DNA. Community profiles were compared using cluster analysis. BIOLOG profiles were primarily influenced by seasonal trends rather than naphthenic acids content. In contrast, phospholipid fatty acid analysis comparisons clustered communities that had higher levels of residual oil, although this association was not strong. In contrast, cluster diagrams produced from the denaturing gradient gel electrophoresis data clearly separated bacterial communities according to naphthenic acids concentrations, indicating that naphthenic acids content was a major influence on the composition of the bacterial community. In addition, denaturing gradient gel electrophoresis profiles indicated that naphthenic

acids-exposed bacterial communities were homogeneous on a scale of meters, whereas unexposed (off-site) wetlands were less homogeneous.

Discovery Description: Naphthenic acids could be used as an alternative method for disinfection of water.

Title: Hydrophobic interaction electrokinetic chromatography for the separation of polycyclic aromatic hydrocarbons using non-aqueous matrices  
Source: JOURNAL OF CHROMATOGRAPHY A 914 (1-2): 223-231 APR 20 2001

Abstract: Capillary electrophoresis methodology is developed to provide a rapid, inexpensive and robust technique for screening polycyclic aromatic hydrocarbons (PAHs) in water using additive complexation. A series of conventional RPLC ion-pairing agents are investigated in three different totally non-aqueous separation solvents, and the relative role of hydrophobic interaction versus electrostatic association is evaluated. Methanol is found to provide optimal selectivity when coupled with the tetrahexylammonium cation providing total analysis times of approximately 15 min for the analysis of thirteen 2-7-ring PAH pollutants. Solid-phase microextraction is demonstrated to be an effective sample preparation technique for extraction/preconcentration of PAHs from water into methanol run buffer prior to injection. (C) 2001 Elsevier Science B.V. All rights reserved.

Discovery Description: Capillary electrophoresis methodology could be employed as a novel water purification technique.

Title: Tissue implanted glucose needle electrodes: early sensor stabilization and achievement of tissue-blood correlation during the run in period

Source: ANALYTICA CHIMICA ACTA

Abstract: In this study, two approaches were utilized to reduce surface fouling and enhance operational reliability of tissue implanted glucose sensors. The first, Open Microflow, used an open cannula incorporated needle electrode. Here, the sensor surface was subjected to slow flow of protein-free fluid (chelate containing isotonic buffer or saline) directly at the

implant site. Positive outcomes of this included reduced stabilization time ( $\leq 90$  min), accelerated “pick up” of tissue glucose changes after intravenous injections of glucose or insulin without the usual reported lag, and high correlation between tissue and blood glucose values under dynamic conditions avoiding the need for in vivo calibration and a reduced surface fouling. Open Microflow fluid composition was important for performance. A range of isotonic solutions were tested; NaCl alone, 4 mM KCl and NaCl, 0.74% (w/v) Na<sub>2</sub>HPO<sub>4</sub> with NaCl or insulin (2 U/1 ml) gave partial correlation with blood glucose, while best agreement was seen with EDTA/phosphate buffer. A second approach evaluated an outer membrane barrier comprising polyurethane precursor (Trixene SC762 (R)) and non-ionic surfactant (2% (v/v) Triton X100). This modified polyurethane conferred good haemo- and tissue biocompatibility with exposure to whole blood confirming low fouling, and for tissue no evident drift during acute monitoring. (c) 2005 Elsevier B.V. All rights reserved.

Discovery Description: Methodologies from Open Microflow or a membrane barrier comprising polyurethane precursor (Trixene SC762 (R)) and non-ionic surfactant (2% (v/v) Triton X100) could be used to prevent fouling of membranes.

Title: Phytoremediation of petroleum-contaminated soils in the tropics - Pre-selection of plant species from eastern Venezuela

Source: JOURNAL OF APPLIED BOTANY AND FOOD QUALITY-ANGEWANDTE BOTANIK

Abstract: Phytoremediation, i.e. the use of plants to recover contaminated soils, is a non-destructive and cost-effective in situ technology. In the case of oil contamination, it is based on the stimulation of petroleum hydrocarbon-degrading microorganisms in the rhizosphere. Investigations about this technology in the tropics are scarce. Before starting time and cost-intensive greenhouse studies, a pre-selection of suitable native plants is indicated. In our work we present an approach to effectively pre-select species for the development and application of phytoremediation of petroleum-contaminated soils. In the eastern savannahs of Venezuela, plant species found on contaminated sites and therefore obviously tolerant of oil pollution were assessed regarding characteristics considered beneficial for their use in phytoremediation, like ease of propagation and favorable root

system characteristics. Fifty-seven native or naturalized species, comprising 18 legumes, 19 grasses, 3 sedges and 17 other herbaceous species were found to occur on contaminated sites. Almost forty percent were found on more than one site. The legumes proved to be the easiest group to propagate, whereas most of the wild grasses and the other herbaceous species could not be propagated successfully. The most favorable root system, i.e. deep-reaching, widely branched roots creating an extended rhizosphere, was found in some grasses and sedges. Legumes had, in general, less ramified but deeper reaching roots. The species selected for further research are some wild legumes and cultivated pasture grasses that are widely used in the tropics. Additionally, some native wild at-asses and one sedge were included. The Study should serve as a basis for further investigations on oil phytoremediation in the tropics.

Discovery Description: Phytoremediation techniques may be employed to purify water.

Title: A novel bioartificial liver with culture of porcine hepatocyte aggregates under simulated microgravity

Source: ARTIFICIAL ORGANS

Abstract: An extracorporeal bioartificial liver device could provide vital support to patients suffering from acute liver failure. We designed a novel, customized bioreactor for use as a bioartificial liver (patent pending). The Innsbruck Bioartificial Liver (IBAL) contains aggregates of porcine hepatocytes grown under simulated microgravity. The culture vessel rotates around its longitudinal axis and is perfused by two independent circuits. The circuit responsible for exchange of plasma components with the patient consists of a dialysis tube winding spirally around the internal wall of the culture vessel. IBAL was evaluated in vitro. Viability tests showed sufficient viability of hepatocytes for up to 10 days. Cytologic examination of samples from the bioreactor showed liver cell aggregates. These were also examined by electron microscopy. A number of biochemical parameters were analyzed. In conclusion, cell culture is possible for at least 10 days in the IBAL system, organoid hepatocyte aggregates are formed and synthetic activity of the hepatocytes was demonstrated.



Discovery Description: An artificial liver may be configured to filter water, or the principles used to create the artificial liver may be utilized to create a water filter.

Title: Uptake of cadmium, lead, nickel and zinc from soil and water solutions by the nickel hyperaccumulator *Berkheya coddii*  
Source: ACTA BIOLOGICA CRACOVIENSIA SERIES BOTANICA  
Abstract: *Berkheya coddii* Roessler (Asteraceae), an endemic herbaceous and perennial nickel-hyperaccumulating plant growing on Ni-enriched ultramafic soils in South Africa, is perceived as a promising species for phytoremediation and phytomining due to its large biomass production and high Ni content. Total concentrations of a number of elements in mature leaves, soil and related bedrock were obtained. The average Ni concentration in leaves was 18,000  $\mu\text{g} \cdot \text{g}^{-1}$  dry mass, whereas in soil and bedrock the total amount of Ni was 1,300  $\mu\text{g} \cdot \text{g}^{-1}$  and 1,500  $\mu\text{g} \cdot \text{g}^{-1}$ , respectively. Exceptionally high average Ni concentrations (55,000  $\pm$  15,000  $\mu\text{g} \cdot \text{g}^{-1}$ ,  $n = 6$ ) were found in *B. coddii* leaves from Songimvelo Game Reserve, including the highest-ever reported concentration of Ni in leaves (76,100  $\mu\text{g} \cdot \text{g}^{-1}$  - maximum value in a single sample). Young plants grown in pots with ultramafic soil accumulated small quantities of Cd, Pb or Zn, but the concentrations of these elements increased after the addition of metal solutions to the soil. Excised shoots immersed in concentrated solutions of Cd, Ni, Pb or Zn accumulated large amounts of these metals in the leaves

Discovery Description: *Berkheya coddii* may be used to remove cadmium, lead, nickel and zinc from water instead of conventional methods used to remove these metals.

Title: Treatment of paint spray booth off-gases in a fungal biofilter  
Source: JOURNAL OF ENVIRONMENTAL ENGINEERING-ASCE  
Abstract: Biological processes, most notably biofilters and biotrickling filters, are increasingly used to remove and biodegrade a wide variety of volatile organic compounds (VOCs) present in gas streams emitted from industrial operations. In the research described herein, a laboratory-scale

biofilter was operated for a period of more than 180 days to treat a waste gas comprised of a four-component VOC mixture representative of solvents present in off-gases emitted by painting operations. The biofilter, packed with a cubed polyurethane foam media and initially inoculated with a pure culture of the fungus *Cladosporium sphaerospermum*, was maintained under acidic conditions throughout the duration of the experiments. The system was supplied with a mixture of n-butyl acetate, methyl ethyl ketone, methyl propyl ketone, and toluene with influent concentrations of 124, 50.5, 174, and 44.6 mg m<sup>-3</sup>, respectively. The biofilter's empty bed residence time (EBRT) was varied from 2.0 min to 15 s. When the influent gas stream was properly humidified, the system exhibited stable long-term performance with an average total VOC removal greater than 98% even with an EBRT as low as 15 s. Under the loading 92 g m<sup>-3</sup> h<sup>-1</sup>, VOC concentration profiles measured along the condition tested, this corresponds to an average elimination capacity of 92 g m<sup>-3</sup> height of the biofilter revealed a distinct VOC degradation pattern that was observed under all loading conditions tested. Although the column was initially inoculated with only *Cladosporium sphaerospermum*, several additional species of fungi tentatively identified as *Penicillium brevicompactum*, *Exophiala jenselmei*, *Fusarium oxysporum*, *Fusarium nygamai*, *Talaromyces flavus*, and *Follsecaea pedrosi* were found growing attached to the packing medium by the end of experiment. Results demonstrate that fungal biofilters can consistently maintain high removal efficiency for paint VOC mixtures over extended periods of operation. The results also indicate that it would be difficult and likely unnecessary to maintain specific species in full-scale fungal biofilters treating paint spray booth emissions.

Discovery Description: Principles from fungal biofilters (the use of biofilters) may be employed to filter water, perhaps water that had been vaporized or turned into a fine mist.

Title: Phytoextraction: Simulating uptake and translocation of arsenic in a soil-plant system

Source: INTERNATIONAL JOURNAL OF PHYTOREMEDIATION

Abstract: The uptake, transport, and accumulation of metals by plants are functions central to successfully to extraction. This study investigates the uptake and translocation of arsenic from a contaminated sandy soil by a

mature Chinese brake fern (*Pteris vittata* L.). An existing mathematical model for the coupled transport of water, heat, and solutes in the soil-plant-atmosphere continuum (CTSPAC) was modified to examine the flow of water as well as the uptake and translocation of total arsenic in the xylem of the fern. This model was calibrated using greenhouse measurements before its application. Simulation results showed that about 20% of the soil arsenic was removed by the fern in 10 d, of which about 90% of the arsenic was stored in the fronds and 10% in the roots. Although arsenic mass in the plant tissues increased consecutively with little, arsenic concentration in the xylem sap of the root tips has a typical diurnal distribution pattern: increasing during the day and decreasing at night, resulting from daily, variations of frond surface water transpiration. The largest difference in simulated arsenic concentration in the root tips between the day and night was about 5%. This study also suggests that the use of transpiration stream concentration factor (TSCF), which is defined as the ratio of chemical concentration in the xylem sap to that in the external solution, to evaluate the translocation efficiency of arsenic for the hyperaccumulator Chinese brake fern (*Pteris vittata* L.) could be limited.

Discovery Description: Phytoremediation techniques may be employed to purify water.

Title: Adhesion of bacterial exopolymers to  $\alpha$ -FeOOH: Inner-sphere complexation of phosphodiester groups

Source: LANGMUIR

Abstract: Extracellular polymeric substances (EPS) constitute a heterogeneous mixture of polyelectrolytes that mediate biomineralization and bacterial adhesion and stabilize biofilm matrixes in natural and artificial environments. Although nucleic acids are exuded extracellularly and are purported to be required for biofilm formation, direct evidence of the active mechanism is lacking. EPS were extracted from both *Bacillus subtilis* (a gram-positive bacterium) and *Pseudomonas aeruginosa* (a gram-negative bacterium) and their interaction with the goethite ( $\alpha$ -FeOOH) surface was studied using attenuated total internal reflection infrared spectroscopy. Correspondence between spectral data and quantum chemical calculations demonstrate that phosphodiester groups of nucleic acids mediate the binding of EPS to mineral surfaces. Our data indicate that these groups emerge from

the EPS mixture to form monodentate complexes with Fe centers on the goethite ( $\alpha$ -FeOOH) surface, providing an energetically stable bond for further EPS or cell adhesion.

Discovery Description: The mechanisms by which extracellular polymeric substances (EPS) mediate biomineralization and bacterial adhesion and stabilize biofilm matrixes could be mimicked to deter fouling or control where it does and does not happen in water purification systems.

Title: Uptake and distribution of selenium in different fern species

Source: INTERNATIONAL JOURNAL OF PHYTOREMEDIATION

Abstract: There has been an interest in using hyperaccumulating plants for the removal of heavy metals and metalloids. High selenium (Se) concentrations in the environment are detrimental to animals, humans, and sustainable agriculture, yet selenium is also an essential nutrient for humans. This experiment it-as conducted to screen fern plants for their potential to accumulate selenium. Eleven fern species, *Pteris vittata*, *P. quadriaurita*, *P. dentata*, *P. ensiformis*, *P. cretica*, *Dryopteris erythrosora*, *Didymochlaena truncatula*, *Adiantum hispidulum*, *Actiniopteris radiata*, *Davallia griffithiana*, and *Cyrtomium fulcatum*, were grown under hydroponic conditions for one week at 20 mg L<sup>-1</sup> selenate or selenite. Root Se concentrations reached 245-731 and 516-1082 mg kg<sup>-1</sup> when treated with selenate and selenite, respectively. The corresponding numbers in the fronds were 153-745 and 74-1,028 mg kg<sup>-1</sup> with no visible toxicity symptoms. Only three fern species it-ere able to accumulate more Se in the fronds than the roots, which were *D. griffithiana* it-hen treated with selenate, *P. vittata* when treated with selenite, and *A. radiata* regardless of the forms of Se. *A. radiata* it-as the best species overall for Se accumulation. More research is needed to further determine the potential of the fern species identified in this study for phytoremediation of the Se contaminated soils and water.

Discovery Description: Phytoremediation techniques may be employed to purify water.

Title: Chemical defenses of seaweeds against microbial colonization

Source: BIODEGRADATION 8 (3): 211-220 1997

Abstract: Any living or non-living surface immersed in seawater rapidly acquires a bacterial biofilm. For living marine organisms, biofilm formation can result in the death of the host, and thus there is strong evolutionary pressure for marine eukaryotes to evolve mechanisms which inhibit or control the development of biofilms on their surfaces. Some marine eukaryotes are indeed successful in controlling biofilms on their surfaces, and in many instances this control is achieved by the production of inhibitory chemicals which act at or near the surface of the organism. In some cases these natural inhibitors are simply toxic to bacteria. However, increasingly it appears that at least some of these compounds act by interfering specifically with bacterial characteristics which effect the ability of bacteria to colonize their hosts, such as attachment, surface spreading, or the production of extracellular macromolecules. As an example, the Australian seaweed *Delisea pulchra* appears to control bacterial colonization by interfering with a bacterial regulatory system (the acylated homoserine lactone system) that regulates several colonization relevant bacterial traits. Understanding how marine organisms control specific bacterial colonization traits should provide us with insights into new technologies for the control of biofilms on artificial surfaces.

Discovery Description: The chemical defenses of these seaweeds may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Antimicrobial activity in sub-Arctic marine invertebrates

Source: POLAR BIOLOGY 26 (9): 591-600 SEP 2003

Abstract: In the marine environment, any living or non-living surface is exposed to bacterial colonization. Many invertebrate species in temperate, tropical and Antarctic regions have demonstrated chemical defenses against the formation of microbial films. In the present study, the antimicrobial activity of sub-Arctic invertebrates was investigated for the first time. Crude extracts of abundant invertebrates belonging to several taxonomic groups were tested for their inhibitory effects on the growth of five sympatric phylogenetically diverse bacterial strains. Six out of 18 (33%) crude extracts inhibited bacterial growth at natural extract concentrations. The crude extract of the sponge *Haliclona viscosa* inhibited growth of all five

bacterial strains, suggesting the presence of metabolites with broad-spectrum activity. Three active compounds were isolated from *H. viscosa* having antibacterial properties similar to those of the crude extract. Our data indicate that antibacterial secondary metabolites are present in sub-Arctic marine invertebrates but are less abundant than in temperate, tropical or Antarctic species.

Discovery Description: The extracts from these marine sponges may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Identification and characterization of a putative transcriptional regulator controlling the expression of fouling inhibitors in *Pseudoalteromonas tunicata*

Source: APPLIED AND ENVIRONMENTAL MICROBIOLOGY 68 (1): 372-378 JAN 2002

Abstract: The dark green pigmented marine bacterium *Pseudoalteromonas tunicata* colonizes living surfaces and produces a range of extracellular compounds that inhibit common fouling organisms, including marine invertebrate larvae, algae, bacteria, and fungi. We have observed a positive correlation between the antifouling activity of *A. tunicata* strain D2 and the expression of pigmentation. To address the hypothesis that pigmentation and antifouling may be jointly regulated in this organism and to begin to identify potential regulatory elements, we used transposon mutagenesis to generate a strain of *A. tunicata* deficient in antifouling activity. The data presented here describe the phenotypic and molecular characterization of a nonpigmented transposon mutant strain of *P. tunicata* (D2W2). Analyses of the antifouling capabilities of D2W2 demonstrate that this strain is deficient in the ability to inhibit each of the target fouling organisms. Genetic analysis of D2W2 identified a gene, designated *wmpR* (white mutant phenotype), with high sequence similarity to transcriptional regulators *ToxR* from *Vibrio cholerae* and *CadC* from *Escherichia coli*. Two-dimensional polyacrylamide gel electrophoresis analysis revealed that *WmpR* is essential for the expression of a significant subset of stationary-phase-induced proteins likely to be important for the synthesis of fouling inhibitors. The identification of a gene involved in the regulation of expression of antifouling phenotypes will contribute to the understanding of the

interactions between bacteria and other surface-colonizing organisms in the marine environment.

Discovery Description: The anti-fouling properties of *Pseudoalteromonas* tunicate may be incorporated into membranes or membrane coatings to deter/prevent fouling.

Title: Growth, compatible solute and salt accumulation of five mycorrhizal fungal species grown over a range of NaCl concentrations

Source: MYCORRHIZA 16 (2): 99-109 MAR 2006

Abstract: The oil sand industry in northeastern Alberta produces vast areas of severely disturbed land. The sodicity of these anthropic soils is one of the principal constraints that impede their revegetation. Previous in vitro studies have shown that the ectomycorrhizal fungi *Laccaria bicolor* (Maire) Orton UAMH 8232 and *Hebeloma crustuliniforme* (Bull) Quel. UAMH 5247 have certain salt-resistant traits and thus are candidate species for the inoculation of tree seedlings to be outplanted on salt-affected soil. In this study, the in vitro development of these fungi was compared to that of three mycorrhizal fungi [*Suillus tomentosus* (Kauff.) Sing., Snell and Dick; *Hymenoscyphus* sp. and *Phialocephala* sp.] isolated from a sodic site created by Syncrude Canada Ltd. Their growth, osmotic and Na/Cl contents were assessed over a range (0, 50, 100, 200 mM) of NaCl concentrations. After 21 days, the two ascomycetes (*Hymenoscyphus* sp. and *Phialocephala* sp.) were shown to be more resistant to the NaCl treatments than the three basidiomycete species. Of the basidiomycetes, *L. bicolor* was the most sensitive to NaCl stress, while *H. crustuliniforme* showed greater water stress resistance, and the *S. tomentosus* isolate exhibited greater Na and Cl filtering capacities and had a better biomass yield over the NaCl gradient tested. Both ascomycetes used mechanisms other than carbohydrate accumulation to palliate NaCl stress. While the *Hymenoscyphus* isolate accumulated proline in response to NaCl treatments, the darker *Phialocephala* isolate may have used compounds such as melanin. The basidiomycete species accumulated mainly mannitol and/or proline in response to increasing concentrations of NaCl.

Discovery Description: The properties of these plants may be used to remove salt from water.

Title: Control of Cl<sup>-</sup> transport in the operculum epithelium of *Fundulus heteroclitus*: long- and short-term salinity adaptation  
Source: BIOCHIMICA ET BIOPHYSICA ACTA-BIOMEMBRANES 1566 (1-2): 129-

Abstract: The euhaline fish, *Fundulus heteroclitus*, adapts rapidly to enhanced salinity by increasing the ion secretion by gill chloride cells. An increase of similar to 70 mOsm in plasma osmolarity was previously found during the transition. To mimic this in vitro, isolated opercular epithelia of seawater-adapted *Fundulus* mounted in a modified Ussing chamber were exposed to an increase in NaCl and/or osmolarity on the basolateral side, which immediately increased I-SC. Various Cl<sup>-</sup> channel blockers as well as the K<sup>+</sup> channel blocker Ba<sup>2+</sup> added to the basolateral side all inhibited the steady-state as well as the hypertonic stimulation of I-SC. The There Exists-agonist isoproterenol stimulates I-SC in standard Ringer solutions. In contrast, when cell volume was kept at the larger value by simultaneous addition of water, the stimulation with isoproterenol was abolished, suggesting that the key process for activation of the Na<sup>+</sup>, K<sup>+</sup>, 2Cl<sup>-</sup> cotransporter is cell shrinkage. The protein kinase C (PKC) inhibitor chelerythrine and the myosin light chain kinase (MLCK) inhibitor ML-7 had strong inhibitory effects on the mannitol activation of I-SC, thus both MLCK and PKC are involved. The two specific protein kinase A (PKA) inhibitors H-89 and KT 5720 had no effect after mannitol addition whereas isoproterenol stimulation was completely blocked by H-89. This indicates that PKA is involved in the activation of the apical Cl<sup>-</sup> channel via c-AMP whereas the shrinkage activation of the Na<sup>+</sup>, K<sup>+</sup>, 2Cl<sup>-</sup> cotransporter is independent of PKA activation. The steady-state Cl<sup>-</sup> secretion was stimulated by an inhibitor of serine/threonine phosphatases of the PP-1 and PP-2A type and inhibited by a PKC inhibitor but not by a PKA inhibitor. Thus, it seems to be determined by continuous phosphorylation and dephosphorylation involving PKC but not PKA. The steady-state Cl<sup>-</sup> secretion and the maximal obtainable Cl<sup>-</sup> secretion were measured in freshwater-adapted fish and in fish retransferred to saltwater. No Is. could be measured in fresh water-adapted fish or in the fish within the first 18 h after transfer to saltwater. As evidenced from Western blot analysis using antiserine-antibodies, a heavily serine phosphorylated protein of about 190 kDa was consistently observed in the saltwater-acclimated fish, but was only weakly present in freshwater-acclimated fish. This observation indicates



that acclimatization to saltwater stimulates the expression of this 190-kDa protein and/or a serine/threonine kinase, which subsequently phosphorylates the protein. (C) 2002 Elsevier Science B.V. All rights reserved.

Discovery Description: The mechanisms this fish uses to deal with salt concentrations may be applicable to how humans could deal (with the aid of drugs derived from these fish etc) with increased salt concentrations in areas where water purification plants/devices are impracticable.

Title: Filamentary coagulation of particles from water-heterogeneous systems in the field of an acoustic resonator

Source: ACOUSTICAL PHYSICS 52 (6): 633-637 DEC 2006

Abstract: The coagulation of particles from water-heterogeneous systems in the field of a confocal ultrasonic resonator is studied. It is found that, at frequencies of several megahertz, when acoustic power of about 1 W is applied to the resonator, long stable filaments consisting of the material of the heterogeneous system are formed in the vicinity of the resonator axis. The filaments consist of thin disks formed by coalescent particles spaced at intervals strictly equal to half of the sound wavelength. The features of this coagulation are determined for suspensions of various nature (metal and dielectric particles, colloidal solutions, and oil emulsions). It is established that the coagulation in a standing acoustic wave occurs faster than under natural conditions (under the influence of gravity). The possibility of using this effect for cleaning liquids from impurities and separating hyperfine particles without employing filter materials is discussed.

Discovery Description: Particles could be coagulated using acoustic technology instead of having to add chemicals to the water in water purification plants, thus saving money and not having to remove potentially harmful chemicals from the water.

Title: Chromium biosorption by thermally treated biomass of the brown seaweed, *Ecklonia* sp.

Source: INDUSTRIAL & ENGINEERING CHEMISTRY RESEARCH

**Abstract:** Biomass of the brown seaweed *Ecklonia* removed both cationic Cr(III) and anionic Cr(VI). The Cr(III) was removed through an ion-exchange mechanism; the Cr(VI) was removed through a redox reaction with the biomass. Among the various pretreatments for developing an efficient biomass, thermal treatment was used in this study. After thermal treatment, the biomass characteristics were investigated using SEM, BET, FTIR, potentiometric titration, and solution analysis. The Cr(III)/Cr(VI) removal performance of the biomass was also examined. The thermal treatment altered the physical and chemical properties of the biomass. The carboxyl groups present in the biomass were decreased to 76% by thermal treatment, but the intraparticle mass transfer resistance increased. These effects of thermal treatment on the biomass reduced the adsorption rate and efficiency of Cr(III) but made the biomass stronger as a Cr(VI) reductant, resulting in an increase in the Cr(VI) reduction rate and the Cr(VI) reducing capacity of the biomass. Therefore, the thermal treatment has to be selectively adopted according to Cr(III) and Cr(VI) concentrations, since it simultaneously reduces and enhances the Cr(III) and Cr(VI) removals, respectively.

**Discovery Description:** This seaweed could be used in a phytoremediation process to remove contaminants from water.

**Title:** Nanostructured designs of biomedical materials: Applications of cell sheet engineering to functional regenerative tissues and organs

**Source:** JOURNAL OF CONTROLLED RELEASE

**Abstract:** Biomaterials surface design is critical for control of cell-materials interactions. Materials surface characteristics important to cell-materials interactions are the following: (a) nonfouling surfaces where cells cannot interact; (b) surfaces that interact with cells but do not alter cell morphology or metabolism (passive adhesion processes); and (c) surfaces that strongly interact with cells and cell-surface receptors to alter cell shape after metabolic interactions (active adhesion). In this paper, we briefly discuss the relationship between materials surface characteristics and cells for biomaterials designs in these categories. We have extensively investigated the thermoresponsive polymer, poly(N-isopropylacrylamide) (PIPAAm), as grafted surfaces allowing recovery of confluent cell monolayers as contiguous living cell sheets for tissue engineering applications. Cellular

interactions with PIPAAm-grafted surfaces can be regulated vertically using the thickness of the PIPAAm-grafted layers in nanometer-scale levels, as well as laterally (spatially) using nano-patterned PIPAAm chemistry on various other surface chemistries. PIPAAm-grafted surfaces with 15-20-nm thick layers exhibit temperature-dependent cell adhesion/detachment control, while surfaces with PIPAAm layer thicknesses of more than 30 nm do not support cell adhesion. These changes in cell adhesion are explained by the limited mobility of the surface grafted polymer chains as a function of grafting, hydration, and temperature. (c) 2004 Elsevier B.V. All rights reserved.

Discovery Description: Because most cells transport water across their cellular membrane and reject other molecules, perhaps a living membrane could be created that would filter water.

Title: Membranes for biohybrid liver support: the behavior of C3A hepatoblastoma cells is dependent on the composition of acrylonitrile copolymers

Source: JOURNAL OF BIOMATERIALS SCIENCE-POLYMER EDITION

Abstract: Co-polymers based on acrylonitrile, N-vinylpyrrolidone, aminoethylmethacrylate and sodium methallylsulfonate were used to prepare flat membranes by phase inversion. The surface properties of membranes were characterized by water contact angle measurements, atomic force microscopy and X-ray photoelectron spectroscopy (XPS). Membrane permeability was estimated by porosity measurements with water as test liquid. Human C3A hepatoblastoma cells were plated on these materials. Cell-material interaction was characterized by overall cell morphology, formation of focal adhesion contacts and intercellular junctions. Furthermore, cell proliferation was measured and compared with the functional activity of cells as indicated by 7-ethoxycoumarin-O-deethylase. More hydrophilic materials reduced spreading of cells, formation of focal adhesion and subsequent proliferation while homotypic cell adhesion was facilitated in correlation with stronger expressions of intercellular junctions and improved functional activity. In contrast, membranes with stronger adhesivity enhanced cell proliferation but reduced the functional activity of cells. It was concluded that the co-polymerisation

of acrylonitrile with hydrophilic co-monomers, such as N-vinylpyrrolidone, could be used to tailor membrane materials for the application in biohybrid liver support systems.

Discovery Description: Because most cells transport water across their cellular membrane and reject other molecules, perhaps a living membrane could be created that would filter water.

Title: Elucidation of functional groups on gram-positive and gram-negative bacterial surfaces using infrared spectroscopy

Source: LANGMUIR

Abstract: Surface functional group chemistry of intact Gram-positive and Gram-negative bacterial cells and their isolated cell walls was examined as a function of pH, growth phase, and growth media (for intact cells only) using attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy. Infrared spectra of aqueous model organic molecules, representatives of the common functional groups found in bacterial cell walls (i.e., hydroxyl, carboxyl, phosphoryl, and amide groups), were also examined in order to assist the interpretation of the infrared spectra of bacterial samples. The surface sensitivity of the ATR-FTIR spectroscopic technique was evaluated using diatom cells, which possess a several-nanometers-thick layer of glycoprotein on their silica shells. The ATR-FTIR spectra of bacterial surfaces exhibit carboxyl, amide, phosphate, and carbohydrate related features, and these are identical for both Gram-positive and Gram-negative cells. These results provide direct evidence to the previously held conviction that the negative charge of bacterial surfaces is derived from the deprotonation of both carboxylates and phosphates. Variation in solution pH has only a minor effect on the secondary structure of the cell wall proteins. The cell surface functional group chemistry is altered neither by the growth phase nor by the growth medium of bacteria. This study reveals the universality of the functional group chemistry of bacterial cell surfaces.

Discovery Description: The fact that the surfaces of bacteria are negatively charged could lead to magnetically charged membranes that would repel bacteria, and hence prevent/deter fouling.

Title: Electric field-induced cell membrane permeabilization and gene transfer: Theory and experiments

Source: ENGINEERING IN LIFE SCIENCES

Abstract: The permeabilization and gene transfer phenomena in terms of the effect of electric field and cell parameters are reviewed in this paper.

Electropermeabilization designates the use of short high-voltage pulses to overcome the barrier of the cell membrane. A position-dependent modulation of the membrane potential difference is induced, leading to a transient and reversible local membrane alteration. The electro-induced permeabilization is long lived. A free exchange of hydrophilic molecules takes place across the membrane. The fraction of the cell surface which is competent for exchange is a function of the field intensity. The level of local exchange is strongly controlled by the pulse duration. This permeabilized state can be used to load cells with a variety of different molecules, either through simple diffusion in the case of small molecules, or through a multistep process as is the case for DNA transfer involving the electrophoretically driven association of the macromolecule with the destabilized membrane and its subsequent passage. Electropermeabilization is now in use for the delivery of a large variety of molecules: from ions to drugs, dyes, tracers, antibodies, oligonucleotides, RNA and DNA. While most studies are performed in vitro in cells in culture, an increasing number of data are obtained in vivo on tissues. However, membrane molecular and cell metabolic changes remain for the most part poorly understood. Therefore it is of great importance to elucidate the underlying phenomena both for the in vitro use of the method in terms of efficiency but also for the in vivo use of the method in terms of security.

Discovery Description: It may be possible to tune membranes using electrical fields so that they are selectively permeable.

Title: Functional feeding groups of Brazilian Ephemeroptera nymphs: ultrastructure of mouthparts

Source: ANNALES DE LIMNOLOGIE-INTERNATIONAL JOURNAL OF LIMNOLOGY

**Abstract:** In order to assign 18 mayfly taxa found in streams in the Macae River basin into Functional Feeding Groups, the anatomy of their feeding apparatus was examined through scanning electron microscopy. Also, habitat preference and field observations of feeding behavior were made to assure FFG assignment. Ephemeropteran taxa were classified into five FFGs: Passive Filterers - *Hylister plaumanni*; Active Filterer *Lachlania boanovae* and *Campylocia* sp.; Brushers - *Askola froehlich*, *Farrodes carioca*, *Hagenulopsis* spp., *Massartela brieri*, *Miroculis firoehlich*, *Miroculis* sp., and *Thraulodes* spp.; Grazers - *Cloeodes* spp.. *Americabaetis* spp.. *Camelobaetidius* spp. and *Baetodes* spp.; Scrapers *Leprohyphes pereirae*, *Leptohyphes* spp., *Tricorythodes* spp. and *Tricorythopsis* spp. Species of the three best represented mayfly families in south-east Brazil were assigned to different FFGs (*Leptophlebiidae* - Brushers *Baetidae*-Grazers and *Leptohyphidae*-Scrapers), with one exception, *Hylister plaumanni* (*Leptophlebiidae* Active filterers). This information is useful to understand the role of mayflies in stream ecosystems, and to help the development of ecological theories for tropical streams.

**Discovery Description:** Examination of the mouthparts of these nymphs may lead to new ways (new membranes, etc) to filter water.

**Title:** A novel separation and preconcentration method for traces of manganese, cobalt, zinc and cadmium using coagulation of colloidal silica  
**Source:** ANALYTICAL SCIENCES

**Abstract:** A separation and preconcentration method has been developed for traces of heavy metals using coagulation of colloidal silica. An appropriate amount of colloidal silica was added to a sample solution, the pH was adjusted to 11 with tetramethylammonium hydroxide solution and calcium chloride solution was then added to coagulate the silica. The coagulated silica and solution were separated by centrifugation, and the silica was then treated with hydrofluoric and perchloric acids. The residue was taken up in dilute nitric acid and subjected to ICP-AES to determine manganese, cobalt, zinc and cadmium. The proposed method was successfully applied to analysis of river-water.

Discovery Description: This methodology may be used to remove these contaminants from water in conventional water purification plants.

Title: The use of *Agrobacterium tumefaciens* immobilized on Amberlite XAD-4 as a new biosorbent for the column preconcentration of iron(III), cobalt(II), manganese(II) and chromium(III)

Source: TALANTA

Abstract: A microorganism *Agrobacterium tumefaciens* as an immobilized cell on a solid support was presented as a new biosorbent for the enrichment of Fe(III), Co(II), Mn(II) and Cr(III) prior to flame atomic absorption spectrometric analysis. Amberlite XAD-4 was used as a support material for column preconcentration. Various parameters such as pH, amount of adsorbent, eluent type and volume, flow rate of sample solution, volume of sample solution and matrix interference effect on the retention of the metal ions have been studied. The optimum pH for the sorption of above mentioned metal ions were about 6, 8, 8 and 6, respectively. The loading capacity of adsorbent for Co(II) and Mn(II) were found to be 29 and 22  $\mu\text{mol g}^{-1}$ , respectively. The recoveries of Fe(III), Co(II), Mn(II) and Cr(III), under the optimum conditions were found to be 99  $\pm$  3, 99  $\pm$  2, 98  $\pm$  3 and 98  $\pm$  3%, respectively, at the 95% confidence level. The limit of detection was 3.6, 3.0, 2.8 and 3.6  $\text{ng ml}^{-1}$  for Fe(III), Co(II), Mn(II) and Cr(III), respectively, by applying a preconcentration factor of 25. The proposed enrichment method was applied for metal ion determination from water samples, alloy samples, infant foods and certified samples such as whey powder (IAEA-155) and aluminum alloy (NBS SRM 85b). The analytes were determined with a relative error lower than 10% in all samples. (C) 2004 Elsevier B.V. All rights reserved.

Discovery Description: *Agrobacterium tumefaciens* may be used as a biosorbent to remove metals from water.

Title: Analysis of constant-current electro-osmotic dewatering

Source: KAGAKU KOGAKU RONBUNSHU

Abstract: An analytical solution of the basic differential equation for a constant-current electro-osmotic dewatering is presented by assuming that

both a modified consolidation coefficient  $C_e$  and an electro-osmotic pressure gradient  $E_{pg}$  are constant. Bentonite was used as an experimental material. Electro-osmotic dewatering of homogeneous bentonite cake was conducted under a constant electric current density  $i$  of 0.125-4 A/m<sup>2</sup>.  $C_e$  and  $E_{pg}$ , both obtained by a fitting method, increase with increasing  $i$ . The final moisture distribution of the material can be explained well by the present theory. The progress of electro-osmotic dewatering can be represented by the average consolidation ratio  $U_c$  as in a mechanical expression. The agreement between calculated and experimental  $U_c$  under the condition  $i < 1$  A/m<sup>2</sup> is satisfactory. The coincidence between theory and experiment for  $i > 1$  A/m<sup>2</sup> is good for the first half of the dewatering process but rather poor for the second half of the process, since the creep deformation of the material is not considered in the basic differential equation.

Discovery Description: It may be possible to remove water from the contaminants (instead of the other way around) using a technique similar to this one.

Title: A crucial role for exopolysaccharide modification in bacterial biofilm formation, immune evasion, and virulence

Source: JOURNAL OF BIOLOGICAL CHEMISTRY

Abstract: Biofilms play an important role in many chronic bacterial infections. Production of an extracellular mixture of sugar polymers called exopolysaccharide is characteristic and critical for biofilm formation. However, there is limited information about the mechanisms involved in the biosynthesis and modification of exopolysaccharide components and how these processes influence bacterial pathogenesis. *Staphylococcus epidermidis* is an important human pathogen that frequently causes persistent infections by biofilm formation on indwelling medical devices. It produces a poly-N-acetylglucosamine molecule that emerges as an exopolysaccharide component of many bacterial pathogens. Using a novel method based on size exclusion chromatography-mass spectrometry, we demonstrate that the surface-attached protein IcaB is responsible for deacetylation of the poly-N-acetylglucosamine molecule. Most likely due to the loss of its cationic character, non-deacetylated poly - acetylglucosamine in an isogenic *icaB* mutant strain was devoid of the ability to attach to the



bacterial cell surface. Importantly, deacetylation of the polymer was essential for key virulence mechanisms of *S. epidermidis*, namely biofilm formation, colonization, and resistance to neutrophil phagocytosis and human antibacterial peptides. Furthermore, persistence of the *icaB* mutant strain was significantly impaired in a murine model of device-related infection. This is the first study to describe a mechanism of exopolysaccharide modification that is indispensable for the development of biofilm-associated human disease. Notably, this general virulence mechanism is likely similar for other pathogenic bacteria and constitutes an excellent target for therapeutic maneuvers aimed at combating biofilm-associated infection.

Discovery Description: Understanding of the ways that biofilms form and bind to surfaces may lead to ways to prevent biofilm formation on water purification device surfaces.

Title: A master regulator for biofilm formation by *Bacillus subtilis*

Source: MOLECULAR MICROBIOLOGY

Abstract: Wild strains of *Bacillus subtilis* are capable of forming architecturally complex communities of cells known as biofilms. Critical to biofilm formation is the *eps* operon, which is believed to be responsible for the biosynthesis of an exopolysaccharide that binds chains of cells together in bundles. We report that transcription of *eps* is under the negative regulation of SinR, a repressor that was found to bind to multiple sites in the regulatory region of the operon. Mutations in *sinR* bypassed the requirement in biofilm formation of two genes of unknown function, *ylbF* and *ymcA*, and *sinI*, which is known to encode an antagonist of SinR. We propose that these genes are members of a pathway that is responsible for counteracting SinR-mediated repression. We further propose that SinR is a master regulator that governs the transition between a planktonic state in which the bacteria swim as single cells in liquid or swarm in small groups over surfaces, and a sessile state in which the bacteria adhere to each other to form bundled chains and assemble into multicellular communities.

Discovery Description: Understanding of the ways that biofilms form and bind to surfaces may lead to ways to prevent biofilm formation on water purification device surfaces.

Title: Specific ion exchange properties of a new porous ion exchange resin having an open-celled monolith structure

Source: KOBUNSHI RONBUNSHU

Abstract: A new porous ion exchange resin having an open-celled monolith structure was prepared and its ion exchange properties were examined. The new ion exchange resin was found to have the following advantages over the conventional ion exchange resins having bead structures. First, the new ion exchange resin has a high adsorption ability for the ions having low selectivity coefficients, and the ion exchange band length is smaller than that of the conventional resins. Second, in an electric field, the rejection time of the ions adsorbed to the new ion exchange resin was about one twentieth of that of the ions containing the conventional resins. These specific properties of the new ion exchange resin are attributable to the quantitative introduction of ion exchange groups into the resin having a uniform open-celled monolith structure.

Discovery Description: This porous ion exchange resin could be used to create new membranes for water separation.

Title: Gramicidin channels

Source: IEEE TRANSACTIONS ON NANOBIOSCIENCE

Abstract: Gramicidin channels are mini-proteins composed of two tryptophan-rich subunits. The conducting channels are formed by the transbilayer dimerization of nonconducting subunits, which are tied to the bilayer/solution interface through hydrogen bonds between the indole NH groups and the phospholipid backbone and water. The channel structure is known at atomic resolution and the channel's permeability characteristics are particularly well defined: gramicidin channels are selective for monovalent cations, with no measurable permeability to anions or polyvalent cations; ions and water move through a pore whose wall is formed by the peptide backbone; and the single-channel conductance and cation selectivity vary

when the amino acid sequence is varied, even though the permeating ions make no contact with the amino acid side chains. Given the amount of experimental information that is available-for both the wild-type channels and for channels formed by amino acid-substituted gramicidin analogues-gramicidin channels provide important insights into the microphysics of ion permeation through bilayer-spanning channels. For the same reason, gramicidin channels constitute the system of choice for evaluating computational strategies for obtaining mechanistic insights into ion permeation through the complex channels formed by integral membrane proteins.

Discovery Description: Gramicidin channels could be used to create new membranes for water separation.

Title: Water transport in the brain: Role of cotransporters

Source: NEUROSCIENCE

Abstract: It is generally accepted that cotransporters transport water in addition to their normal substrates, although the precise mechanism is debated; both active and passive modes of transport have been suggested. The magnitude of the water flux mediated by cotransporters may well be significant: both the number of cotransporters per cell and the unit water permeability are high. For example, the Na<sup>+</sup>-glutamate cotransporter (EAAT1) has a unit water permeability one tenth of that of aquaporin (AQP).

1. Cotransporters are widely distributed in the brain and participate in several vital functions: inorganic ions are transported by K<sup>+</sup>-Cl<sup>-</sup> and Na<sup>+</sup>-K<sup>+</sup>-Cl<sup>-</sup> cotransporters, neurotransmitters are reabsorbed from the synaptic cleft by Na<sup>+</sup>-dependent cotransporters located on glial cells and neurons, and metabolites such as lactate are removed from the extracellular space by means of H<sup>+</sup>-lactate cotransporters. We have previously determined water transport capacities for these cotransporters in model systems (*Xenopus* oocytes, cell cultures, and in vitro preparations), and will discuss their role in water homeostasis of the astroglial cell under both normo- and pathophysiological situations. Astroglia is a polarized cell with EAAT localized at the end facing the neuropil while the end abutting the circulation is rich in AQP4. The water transport properties of EAAT suggest a new model for volume homeostasis of the extracellular space during neural activity. (C) 2004 IBRO. Published by Elsevier Ltd. All rights reserved.

Discovery Description: Cotransporters and their mechanisms for water transport could be used to create new membranes for water separation.

Title: Transport properties of cellulose ester membranes for separating gas and liquid mixtures

Source: RUSSIAN JOURNAL OF APPLIED CHEMISTRY

Abstract: Mass-exchange characteristics of cellulose myristate or acetomyristate membranes in separating aqueous-organic, organic, or gas mixtures, particularly, in recovering aromatic hydrocarbons from binary mixtures with aliphatic alcohols, and also ethyl acetate from a mixture of esterification products, are studied.

Discovery Description: Cellulose ester membranes and their mechanisms for water transport could be used to create new membranes for water separation.

Title: "Sorp-vection": An unusual membrane-based separation

Source: AIChE JOURNAL

Abstract: A nonstandard membrane process is described that involves, highly selective sorption of a compound "A" at a large absolute weight fraction  $w(A)$ . coupled with a significant diffusively induced flux of a second component "B." The flux of B convectively moves A from a dilute external mass fraction relative to component B upstream to an enriched mass fraction downstream. The general form of the process has potential applications involving dilute feeds where current membranes processes perform poorly for such removal as a result of excessive solubility of the smaller component B. The most important widespread application is expected to be the separation of small organic solutes from supercritical carbon dioxide to facilitate the recycling and reuse of CO<sub>2</sub> while minimizing costly and energy-intensive recompression steps. We consider the utility of this concept by modeling the separation efficiency of phenol from supercritical carbon, dioxide. (c) 2005 American Institute of Chemical Engineers.

Discovery Description: Sorp-vection could be used as a new method for water purification/separation.

Title: Prostaglandin-dependent osmotic water permeability of the frog and trout urinary bladder

Source: COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY A-MOLECULAR AND INTEGRATIVE PHYSIOLOGY 121 (1): 59-66 SEP 1998

Abstract: Washout of autacoids from serosal Ringer solution, using a repeated change of the solution of the frog and trout urinary bladder, was accompanied by a pronounced rise in the osmotic water permeability: the water transport in the frog rose from  $0.05 \pm 0.02$  to  $1.21 \pm 0.26 \mu\text{l min}^{-1} \cdot \text{cm}^{-2}$ , in the trout, from  $0.041 \pm 0.011$  to  $0.26 \pm 0.034 \mu\text{l min}^{-1} \cdot \text{cm}^{-2}$ . Such an increase in the osmotic water permeability in the trout and frog urinary bladder occurred in the background of a decrease in the prostaglandin E-2 concentration in the serosal Ringer solution. This permeability increase was accompanied by the formation of aggregates of intramembranous particles in the apical plasma membrane of the trout and frog urinary bladder. A decrease in the osmotic water permeability was achieved by the addition to the serosal Ringer solution of  $10^{-8}$  M prostaglandin. Experiments on the frog urinary bladder have shown that prostaglandins E-1, I-2 and F-2 alpha also decrease the osmotic water permeability. Vasotocin increased the osmotic water permeability in the frog urinary bladder but did not affect the osmotic water permeability of the trout urinary bladder. The data obtained indicates a role of the endogenous prostaglandin production in maintaining the low osmotic water permeability in the frog and trout urinary bladder. A suggestion is made that in the vertebrate evolution, colonisation of the fresh-water was connected with the maintenance of the low osmotic water permeability via participation of prostaglandins, whereas the vasotocin hydroosmotic effect developed in the vertebrate evolution later and provided for the possibility of the water absorption, osmotic homeostasis and animal migration from fresh-water to the Land. (C) 1998 Elsevier Science Inc. All rights reserved.

Discovery Description: The frog and trout urinary bladder and the mechanisms that they use to control water flow across them may be used to create new methodologies for filtering water, or possibly new membranes.

Title: Hyperosmoregulation in the red freshwater crab *Dilocarcinus pagei* (Brachyura, Trichodactylidae): structural and functional asymmetries of the posterior gills

Source: JOURNAL OF EXPERIMENTAL BIOLOGY

Abstract: The osmotic and ionic status of the haemolymph and the structural and ion-transport characteristics of the posterior gills of *Dilocarcinus pagei*, a hololimnetic, crab, were investigated. Haemolymph osmolality was  $386 \pm 18$  mosmol kg<sup>-1</sup>, while [Na<sup>+</sup>] and [Cl<sup>-</sup>] were  $190 \pm 13$  and  $206 \pm 12$  mmol l<sup>-1</sup>, respectively; [K<sup>+</sup>], [Ca<sup>2+</sup>] and [Mg<sup>2+</sup>], were  $9.7 \pm 0.7$ ,  $10.2 \pm 0.5$  and  $2.8 \pm 0.4$  mmol l<sup>-1</sup>, respectively (means  $\pm$  S.E.M., N=12-17). The gill lamellae possess a central, osmiophilic area, which exhibits a marked structural asymmetry. The thick (18-20  $\mu$ m) proximal epithelium is characterized by basal invaginations and a few apical vesicles, while the thin (3-10  $\mu$ m) distal epithelium consists of apical pillar cell flanges populated by vesicles and membrane invaginations. Isolated gills, bathed and perfused with NaCl saline, spontaneously generate a negative transbranchial potential difference ( $V_{te}$ ), which stabilises at positive or negative values. Ouabain shifts  $V_{te}$  to more positive values. When mounted in an Ussing chamber, distal split lamellae generate a negative, Cl<sup>-</sup>-dependent short-circuit current ( $I_{sc}$ ). Na<sup>+</sup> substitution leads to more negative values of  $I_{sc}$ . Internal ouabain is without effect, while diphenylamine-2-carboxylate and acetazolamide abolish  $I_{sc}$ . Proximal split lamellae show a positive, Na<sup>+</sup>-dependent  $I_{sc}$ , which decreases after internal application of ouabain. These data suggest that the thin epithelium actively absorbs Cl<sup>-</sup>, while the thick epithelium actively absorbs Na<sup>+</sup>.

Discovery Description: Characteristics of the posterior gills of *Dilocarcinus pagei* and the mechanisms that they use to control water flow across them may be used to create new methodologies for filtering water, or possibly new membranes.

Title: Ultrastructural changes in the gill epithelium of the crab *Chasmagnathys granulatus* (Decapoda : Grapsidae) in diluted and concentrated seawater

Source: MARINE BIOLOGY

Abstract: *Chasmagnathus granulatus* Dana, 1851 is an intertidal estuarine crab that experiences acute salinity changes ranging from < 1 parts per thousand to full-strength seawater and even hypersaline waters in tide pools concentrated by evaporation. Ultrastructural changes induced by salinity in the posterior gills were examined in crabs collected from the Rio de la Plata estuary Argentina during March 1999. The posterior gills of *C. granulatus* are involved both in ion uptake and ion secretion depending on the acclimation medium. These organs are mostly lined with a thick tissue, which presents the characteristics of a typical salt-transporting epithelium. Electron microscopy analysis of gill tissue from crabs acclimated to dilute, full, and concentrated seawater (12 parts per thousand, 34 parts per thousand, and 45 parts per thousand salinity) showed significant development of basolateral membrane interdigitations, with numerous mitochondria and conspicuous apical membrane infoldings. Morphometrical analysis indicated that the subcuticular space delimited by the infolding of the apical membrane was significantly increased in the gills of high-salinity acclimated crabs. Septate junctions, which are thought to define the paracellular permeability, were significantly shorter in high-salinity acclimated crabs, suggesting a possible role of the paracellular pathway in salt secretion.

Discovery Description: Characteristics of the posterior gills of *C. granulatus* and the mechanisms that they use to control water/salt flow across them may be used to create new methodologies for filtering water, or possibly new membranes.

Title: Electrophysiology of posterior, NaCl-absorbing gills of *Chasmagnathus granulatus*: rapid responses to osmotic variations

Source: JOURNAL OF EXPERIMENTAL BIOLOGY

Abstract: In the present study, the influence of short-term osmotic variations on some electrophysiological properties related to NaCl absorption across posterior gills of *Chasmagnathus granulatus* was investigated. The transepithelial potential difference ( $V_{te}$ ) of isolated and perfused gills increased significantly when hyposmotic saline (699 mosmol l<sup>-1</sup>) was used

instead of isosmotic solution (1045 mosmol l(-1)). A reduction of the concentration of Na<sup>+</sup> or Cl<sup>-</sup> at constant osmolarity did not produce any change in V-te. Transepithelial short-circuit current (I-sc) and conductance (G(te)), measured with split gill lamellae mounted in a modified Ussing chamber, also increased after changing to hyposmotic salines (I-sc: from -89.0+/-40.8 mucm(-2) to -179.3+/-37.0 mucm(-2); G(te): from 40.5+/-16.9 mS cm(-2) to 47.3+/-15.8 mS cm(-2)). The observed effects of reduced osmolarity were fast, reversible and gradually dependent on the magnitude of the osmotic variation. The activity of the Na<sup>+</sup>/K<sup>+</sup>-ATPase increased significantly after perfusion with hyposmotic saline, from 18.73+/-6.35 mumol P-i h(-1) mg(-1) to 41.84+/-14.54 mumol P-i h(-1) mg(-1). Theophylline maintained part of the elevated V-te induced by hyposmotic saline, suggesting that an increased cellular cyclic AMP level is involved in the response to reduced osmolarity. In summary, the results indicate that the hemolymph osmolarity regulates active transbranchial NaCl absorption by modulating the activity of the basolateral Na<sup>+</sup>/K<sup>+</sup>-ATPase and by changing a conductive pathway, probably at the apical membrane.

Discovery Description: Properties related to NaCl absorption across posterior gills of *Chasmagnathus granulatus* could be utilized to create new ways to remove salt from water.

Title: Biology of the 2Na(+)/1H(+) antiporter in invertebrates

Source: JOURNAL OF EXPERIMENTAL ZOOLOGY

Abstract: The functional expression of membrane transport proteins that are responsible for exchanging sodium and protons is a ubiquitous phenomenon. Among vertebrates the Na<sup>+</sup>/H<sup>+</sup> antiporter occurs in plasma membranes of polarized epithelial cells and non-polarized cells such as red blood cells, muscle cells, and neurons, and in each cell type the transporter exchanges one sodium for one hydrogen ion, is inhibited by amiloride, and regulates intracellular pH and sodium concentration within tight limitations. In polarized epithelial cells this transporter occurs in two isoforms, each of which is restricted to either the brush border or basolateral cell membrane, and perform somewhat different tasks in the two locations. In prokaryotic cells, sodium/proton exchange occurs by an electrogenic 1Na(+)/2H(+) antiporter that is coupled to a primary active proton pump and together these two proteins are capable of tightly regulating the intracellular concentrations



of these cations in cells that may occur in environments of 4 M NaCl or pH 10-12; Invertebrate epithelial cells from the gills, gut, and kidney also exhibit electrogenic sodium/proton exchange, but in this instance the transport stoichiometry is  $2\text{Na}^{+}/1\text{H}^{+}$ . As with vertebrate electroneutral  $\text{Na}^{+}/\text{H}^{+}$  exchange, the invertebrate transporter is inhibited by amiloride, but because of the occurrence of two external monovalent cation binding sites, divalent cations are able to replace external sodium and also be transported by this system. As a result, both calcium and divalent heavy metals, such as zinc and cadmium, are transported across epithelial brush border membranes in these animals and subsequently undergo a variety of biological activities once accumulated within these cells. Absorbed epithelial calcium in the crustacean hepatopancreas may participate in organismic calcium balance during the molt cycle and accumulated heavy metals may undergo complexation reactions with intracellular anions as a detoxification mechanism. Therefore, while the basic process of sodium/proton exchange may occur in invertebrate cells, the presence of the electrogenic  $2\text{Na}^{+}/1\text{H}^{+}$  antiporter in these cells allows them to perform a wide array of functions without the need to develop and express additional specialized transport proteins. (C) 2001 Wiley-Liss, Inc.

Discovery Description: The  $\text{Na}^{+}/\text{H}^{+}$  antiporter could be studied to the mechanisms by which sodium is transported to determine if it has applicability to new salt removal techniques.

Title: Cellular composition and ultrastructure of the gill epithelium of larval and adult lampreys - Implications for osmoregulation in fresh and seawater  
Source: JOURNAL OF EXPERIMENTAL BIOLOGY

Abstract: Lampreys, one of the only two surviving groups of agnathan (jawless) vertebrates, contain several anadromous species that, during their life cycle, thus migrate from fresh to seawater and back to freshwater. Lampreys have independently evolved the same overall osmoregulatory mechanisms as the gnathostomatous (jawed) and distantly related teleost fishes. Lamprey gills thus likewise play a central role in taking up and secreting monovalent ions. However, the ultrastructural characteristics and distribution of their epithelial cell types [ammocoete mitochondria-rich (MR) cell, intercalated MR cell, chloride cell and pavement cell] differ in several respects from those of teleosts. The ultrastructural characteristics of

these cells are distinctive and closely resemble those of certain ion-transporting epithelia in other vertebrates, for which the function has been determined. The data on each cell type, together with the stage in the life cycle at which it is found, i.e. whether in fresh or seawater, enable the following proposals to be made regarding the ways in which lampreys use their gill epithelial cells for osmoregulating in hypo- and hypertonic environments. In freshwater, the intercalated MR cell takes up  $\text{Cl}^-$  and secretes  $\text{H}^+$ , thereby facilitating the uptake of  $\text{Na}^+$  through pavement cells. In seawater, the chloride cell uses a secondarily active transcellular transport of  $\text{Cl}^-$  to provide the driving force for the passive movement of  $\text{Na}^+$  through leaky paracellular pathways between these cells.

Discovery Description: Lamprey gills could be studied for the purpose of creating new mechanisms for purifying water, or new membranes.

## **12-B. Unvetted Discoveries Obtained Using Literature-based Discovery via Document and Concept Matching in Latent Semantic Indexing Space Using Minimal Spanning Trees**

Title: Combining nonthermal technologies to control foodborne microorganisms

Source: International Journal of Food Microbiology

Abstract: Novel nonthermal processes, such as high hydrostatic pressure (HHP), pulsed electric fields (PEFs), ionizing radiation and ultrasonication, are able to inactivate microorganisms at ambient or sublethal temperatures. Many of these processes require very high treatment intensities, however, to achieve adequate microbial destruction in low-acid foods. Combining nonthermal processes with conventional preservation methods enhances their antimicrobial effect so that lower process intensities can be used. Combining two or more nonthermal processes can also enhance microbial inactivation and allow the use of lower individual treatment intensities. For conventional preservation treatments, optimal microbial control is achieved through the hurdle concept, with synergistic effects resulting from different components of the microbial cell being targeted simultaneously. The mechanisms of inactivation by nonthermal processes are still unclear; thus, the bases of synergistic combinations remain speculative. This paper reviews literature on the antimicrobial efficiencies of nonthermal processes combined with conventional and novel nonthermal technologies. Where possible, the proposed mechanisms of synergy is mentioned.

Discovery Description: Synergistic combinations of sub-lethal disinfectant methodologies might be used in water purification.

Title: Study and application of herbal disinfectants in China

Source: Biomedical and Environmental Sciences

Abstract: Disinfection means killing or removing pathogenic microorganisms in media to realize a harmless process. A disinfectant, which is also referred to as a disinfection medicine in relevant regulations, is the medicine used to kill microorganisms for the purpose of disinfection. The disinfectants prepared from plants (including traditional Chinese herbal

medicines) and the extracts thereof are called herbal disinfectants([1]). China has a long history of using herbal disinfectants. As early as in 533 A.D., the use of Cornel to sterilize well water was recorded in Necessary Techniques for Qi People by Jia Enxie of the Beiwei Dynasty([2]). During the Dragon Boat Festival, people often use fumigants made of traditional Chinese herbal medicines like Chinese Atractylodes, Argy Wormwood Leaf and Red Arsenic Sulfide to smoke their houses, so as to ward off plagues and drive away evils([3]). In fact this is now a kind of disinfection practice.

Discovery Description: Little know constituents of Chinese herbal disinfectants might offer an alternative means of water disinfection.

Title: Reversible antifouling effect of the cyclotide cycloviolacin O2 against barnacles.

Source: J Nat Prod

Abstract: Cycloviolacin O2, a plant peptide of the cyclotide family, is shown to have potent effects against fouling barnacles (*Balanus improvisus*), with complete inhibition of settlement at a concentration of 0.25 microM. The effect of cycloviolacin O2 against barnacles is reversible and nontoxic in the bioassay employed in these studies. Cycloviolacin O2 was isolated from the terrestrial plant *Viola odorata* by strong cation exchange and reversed-phase HPLC and identified by mass spectrometry following aminoethylation and enzymatic cleavage.

Discovery Description: Cycloviolacin O2 may offer a non-toxic means of controlling membrane fouling.

Title: Influence of temperature on the physiological responses of the bivalve *Brachidontes striatulus* and its significance in fouling control.

Source: Mar Environ Res

Abstract: Heat treatment offers an alternative method of fouling control to chlorination in power plants. In order to optimise such a procedure it is important to understand the responses of fouling organisms to elevated water temperatures. In this paper we report results of experiments on the lethal and sub-lethal effects of temperature on the bivalve *Brachidontes striatulus* which is one of the major foulants in the process seawater heat exchangers

of Madras Atomic Power Station located at Kalpakkam, on the east coast of India. The important physiological activities, such as, oxygen consumption, filtration rate, byssus thread production and faecal matter production were studied at temperatures varying from 20 to 38 degrees C. Three different size groups [3-5 mm shell length (group 1), 6-10 mm (group 2), 11-15 mm (group 3)] of *B. striatulus* were used for the experiments. The results showed physiological activities were maximum at 35 degrees C, minimum at 20 and 38 degrees C. Physiological activities increased with size except for byssus thread production, which did not show any trend. Survival times showed a reduction from 30 h at 39 degrees C to 1 h at 45 degrees C and were independent of body size.

Discovery Description: Low temperature heat treatment might offer an alternative to chlorine fouling control in certain cases.

Title: Myoglobin clearance by super high-flux hemofiltration in a case of severe rhabdomyolysis: a case report

Source: CRITICAL CARE

Abstract: Objective To test the ability of a novel super high-flux (SHF) membrane with a larger pore size to clear myoglobin from serum. Setting The intensive care unit of a university teaching hospital. Subject A patient with serotonin syndrome complicated by severe rhabdomyolysis and oliguric acute renal failure Method Initially continuous veno-venous hemofiltration was performed at 2 l/hour ultrafiltration (UF) with a standard polysulphone 1.4 m(2) membrane (cutoff point, 20 kDa), followed by continuous veno-venous hemofiltration with a SHF membrane (cutoff point, 100 kDa) at 2 l/hour UF, then at 3 l/hour UF and then at 4 l/hour UF, in an attempt to clear myoglobin. Results The myoglobin concentration in the ultrafiltrate at 2 l/hour exchange was at least five times greater with the SHF membrane than with the conventional membrane (>100,000 mu g/l versus 23,003 mu g/l). The sieving coefficients with the SHF membrane at 3 l/hour UF and 4 l/hour UF were 72.2% and 68.8%, respectively. The amount of myoglobin removed with the conventional membrane was 1.1 g/day compared with 4.4-5.1 g/day for the SHF membrane. The SHF membrane achieved a clearance of up to 56.4 l/day, and achieved a reduction in serum myoglobin concentration from >100,000 mu g/l to 16,542 mu g/l in 48 hours. Conclusions SHF hemofiltration achieved a much greater clearance of

myoglobin than conventional hemofiltration, and it may provide a potential modality for the treatment of myoglobinuric acute renal failure.

Discovery Description: Super high flux membranes might offer an alternative means of waqter purification.

Title: A mathematical process model for cadmium precipitation by sulfate-reducing bacterial biofilms.

Source: BIODEGRADATION.

Abstract: Sulfate-reducing bacterial (SRB) biofilms were grown in a flowcell in which the biofilm was grown on a fixed area of support which was supplied with recirculating medium of defined composition, volume and circulation rate. Utilization rates for substrates, production rates for products and material mass-balances for substrates and Cd were determined and a mathematical model constructed based on theoretical considerations and experimental data. The rate of sulfate reduction was zero-order with respect to sulfate concentration and unaffected by the presence of 250 microM Cd. However, Cd reacted with the sulfide produced by the SRB to produce solid CdS, removing sulfide from solution. A significant fraction of colloidal CdS was formed which flocculated relatively slowly, limiting the overall rate of Cd bioprecipitation. Experiments using chemically-synthesised colloidal CdS indicated that the biofilm did not influence colloidal Cd flocculation but stimulated sedimentation of the CdS precipitate once flocculated. A mathematical model of bioprecipitation was developed in which the CdS formation rate was determined by two steps: sulfide production by the biofilm and colloidal CdS flocculation. This model accurately predicted the behaviour of further experimental runs which indicated the adequacy of the overall process description. The model also indicated that the rate of sulfate reduction and the rate of flocculation were the key variables in optimising the biofilm system for metal removal.

Discovery Description: Optimization of biofilm-based metal removal via sulfate reduction and flocculation adjustment.

Title: Structural activity relationship studies of zebra mussel antifouling and antimicrobial agents from verongid sponges.

Source: J Nat Prod

**Abstract:** Several dibromotyramine derivatives including moloka'iamine were selected as potential zebra mussel (*Dreissena polymorpha*) antifoulants due to the noteworthy absence of fouling observed on sponges of the order Verongida. Sponges of the order Verongida consistently produce these types of bromotyrosine-derived secondary metabolites. Previously reported antifouling data for the barnacle *Balanus amphitrite* ( $EC_{50} = 12.2 \text{ } \mu\text{M}$ ) support the results reported here that the compound moloka'iamine may be a potential zebra mussel antifoulant compound ( $EC_{50} = 10.4 \text{ } \mu\text{M}$ ). The absence of phytotoxic activity of the compound moloka'iamine toward *Lemna paucicostata* and, most importantly, the compound's significant selectivity against macrofouling organisms such as zebra mussels suggest the potential utility of this compound as a naturally derived antifoulant lead.

**Discovery Description:** Moloka'iamine or other dibromotyramine derivatives may offer natural anti-fouling mechanisms in membrane-based water purification.

**Title:** New imidazole alkaloids from the Indonesian sponge *Leucetta chagosensis*.

Source: J Nat Prod

**Abstract:** Chemical investigation of the sponge *Leucetta chagosensis* collected in Indonesia afforded five new imidazole alkaloids, naamine F (2), naamine G (3), kealiinine A (6), kealiinine B (7), and kealiinine C (8), in addition to the known compound naamine A (1). Naamine G (3) exhibited strong antifungal activity against the phytopathogenic fungus *Cladosporium herbarum* and also showed mild cytotoxicity against mouse lymphoma (L5178Y) and human cervix carcinoma (HeLa) cell lines. In the brine shrimp assay, kealiinine A (6) was more active than naamine G (3). The structures of the new compounds were unambiguously established by 1D and 2D NMR and MS data.

Discovery Description: Extractants from *Leucetia chagosensis* might offer natural deactivation strategies for pathogens such as *Cladosporium herbarum*.

Title: Deficient UDP-glucuronosyltransferase detoxification enzyme activity in the small intestinal mucosa of patients with coeliac disease.

Source: Aliment Pharmacol Ther

Abstract: Small intestinal malignancies in humans are rare; however, patients with coeliac disease have a relatively high risk for such tumours. Intestinal UDP-glucuronosyltransferases are phase II drug metabolism enzymes also involved in the detoxification of ingested toxins and carcinogens. As many toxins and carcinogens are ingested via food, the human gastrointestinal tract not only has an important role in the uptake of essential nutrients, but also acts as a first barrier against such harmful constituents of the food. Therefore, the gastrointestinal mucosa contains high levels of detoxification enzymes such as cytochromes-P450, glutathione S-transferases and UDP-glucuronosyltransferases. AIM: To compare the UDP-glucuronosyltransferase detoxification capacity in small intestinal mucosa of patients with coeliac disease vs. that in normal controls. METHODS: We assessed UDP-glucuronosyltransferase enzyme activities towards 4-methylumbelliferone in small intestinal biopsies of patients with coeliac disease (n = 22) and age- and sex-matched controls (n = 27). RESULTS: Small intestinal UDP-glucuronosyltransferase enzyme activity in controls was significantly higher than in patients with coeliac disease: 0.55 +/- 0.27 vs. 0.35 +/- 0.16 nmol/min mg protein, respectively (mean +/- s.d., P = 0.005). DISCUSSION: The low small intestinal UDP-glucuronosyltransferase detoxification activity in patients with coeliac disease may result in a deficient detoxification of potential carcinogens, and thus could explain in part the relatively high small intestinal cancer risk in these patients.

Discovery Description: Detoxification enzymes such as cytochromes-P450, glutathione S-transferases and UDP-glucuronosyltransferases might be able to aid in pathogenic deactivation in water treatment.

Title: Regulation of UDP glucuronosyltransferases in the gastrointestinal tract



Source: Toxicol Appl Pharmacol

**Abstract:** The UDP glucuronosyltransferases (UGT) of the gastrointestinal (GI) tract have a crucial role in protection against the toxic effects of lipophilic chemicals in the environment. UGTs such as UGT1A7, UGT1A8, and UGT1A10 are exclusively expressed in gastrointestinal tissues, each with a unique tissue distribution pattern that is subject to interindividual variation. The factors regulating this tissue-specific expression and that contribute to variability are beginning to be elucidated. Studies on the UGT1A7, 1A8, 1A9, and 1A10 gene promoters in Caco-2 cells, an in vitro model of enterocytes of the gastrointestinal tract, have identified the caudal homeodomain transcription factor, Cdx2, as an important regulator of the UGT1A8 and 1A10 gene proximal promoters. This transcription factor is found exclusively in the small intestine and colon: it is absent in the gastric epithelium and the esophagus. Cdx2 regulates the UGT1A8 and 1A10 promoters in cooperation with hepatocyte nuclear factor 1alpha (HNF1alpha). It is noteworthy that UGT1A7 is not expressed in gastrointestinal tissue distal to the gastric mucosa and does not contain a Cdx2 binding site in its proximal promoter. Transcription factors, including Sp1, which differentially bind to the initiator regions of the UGT1A8, 1A9, and 1A10 promoters, also contribute to the differences in expression of these UGTs in Caco-2 cells. The identification of important regulatory regions of UGT genes expressed in the gastrointestinal tract, and the transcription factors that bind to these regions, will aid in the elucidation of factors that contribute to interindividual differences in gastrointestinal UGT expression. In turn, this will lead to further understanding of interindividual variation in the capacity of the GI tract to metabolize lipophilic chemicals and to act as a barrier to dietary toxins and orally administered drugs.

**Discovery Description:** UDP glucuronosyltransferases (UGT) may provide a means for removal of or protection from lipophilic environmental compounds.

**Title:** Drug transfer and metabolism by the human placenta.

Source: Clin Pharmacokinet

**Abstract:** The major function of the placenta is to transfer nutrients and oxygen from the mother to the foetus and to assist in the removal of waste products from the foetus to the mother. In addition, it plays an important role in the synthesis of hormones, peptides and steroids that are vital for a successful pregnancy. The placenta provides a link between the circulations of two distinct individuals but also acts as a barrier to protect the foetus from xenobiotics in the maternal blood. However, the impression that the placenta forms an impenetrable obstacle against most drugs is now widely regarded as false. It has been shown that nearly all drugs that are administered during pregnancy will enter, to some degree, the circulation of the foetus via passive diffusion. In addition, some drugs are pumped across the placenta by various active transporters located on both the fetal and maternal side of the trophoblast layer. It is only in recent years that the impact of active transporters such as P-glycoprotein on the disposition of drugs has been demonstrated. Facilitated diffusion appears to be a minor transfer mechanism for some drugs, and pinocytosis and phagocytosis are considered too slow to have any significant effect on fetal drug concentrations. The extent to which drugs cross the placenta is also modulated by the actions of placental phase I and II drug-metabolising enzymes, which are present at levels that fluctuate throughout gestation. Cytochrome P450 (CYP) enzymes in particular have been well characterised in the placenta at the level of mRNA, protein, and enzyme activity. CYP1A1, 2E1, 3A4, 3A5, 3A7 and 4B1 have been detected in the term placenta. While much less is known about phase II enzymes in the placenta, some enzymes, in particular uridine diphosphate glucuronosyltransferases, have been detected and shown to have specific activity towards marker substrates, suggesting a significant role of this enzyme in placental drug detoxification. The increasing experimental data on placental drug transfer has enabled clinicians to make better informed decisions about which drugs significantly cross the placenta and develop dosage regimens that minimise fetal exposure to potentially toxic concentrations. Indeed, the foetus has now become the object of intended drug treatment. Extensive research on the placental transfer of drugs such as digoxin and zidovudine has assisted with the safe treatment of the foetus with these drugs in utero. Improved knowledge regarding transplacental drug transfer and metabolism will result in further expansion of pharmacological treatment of fetal conditions.

**Discovery Description:** Study of placenta-based pathogenic removal might provide new strategies for the design of water purification membranes.

Title: Fate of inhaled particles after interaction with the lung surface.

Source: Paediatr Respir Rev

Abstract: Inhaled particles may cause increased pulmonary and cardiovascular morbidity and mortality. The wall structures of airways and alveoli act as a series of structural and functional barriers against inhaled particles. Deposited particles are displaced and come into close association with epithelial cells, macrophages and dendritic cells. The cellular interplay after particle deposition in a triple cell co-culture model of the human airway wall was investigated by laser scanning microscopy. Furthermore, the cellular response was determined by measurement of TNF-alpha. Dendritic cells gained access to the apical side of the epithelium where they sampled particles and interacted with macrophages.

Discovery Description: Wall structures of airways and alveoli may be mimicked and used as an alternative means of particul filtration from water sources.

Title: Thin and strong! The bioengineering dilemma in the structural and functional design of the blood-gas barrier.

Source: Physiol Rev

Abstract: In gas exchangers, the tissue barrier, the partition that separates the respiratory media (water/air and hemolymph/blood), is exceptional for its remarkable thinness, striking strength, and vast surface area. These properties formed to meet conflicting roles: thinness was essential for efficient flux of oxygen by passive diffusion, and strength was crucial for maintaining structural integrity. What we have designated as "three-ply" or "laminated tripartite" architecture of the barrier appeared very early in the evolution of the vertebrate gas exchanger. The design is conspicuous in the water-blood barrier of the fish gills through the lungs of air-breathing vertebrates, where the plan first appeared in lungfishes (Dipnoi) some 400 million years ago. The similarity of the structural design of the barrier in respiratory organs of animals that remarkably differ phylogenetically, behaviorally, and ecologically shows that the construction has been highly conserved both vertically and horizontally, i.e., along and across the

evolutionary continuum. It is conceivable that the blueprint may have been the only practical construction that could simultaneously grant satisfactory strength and promote gas exchange. In view of the very narrow allometric range of the thickness of the blood-gas barrier in the lungs of different-sized vertebrate groups, the measurement has seemingly been optimized. There is convincing, though indirect, evidence that the extracellular matrix and particularly the type IV collagen in the lamina densa of the basement membrane is the main stress-bearing component of the blood-gas barrier. Under extreme conditions of operation and in some disease states, the barrier fails with serious consequences. The lamina densa which in many parts of the blood-gas barrier is 50 nm thin is a lifeline in the true sense of the word.

Discovery Description: laminated tripartite barrier structures may offer an improved design mechanism for water purification membranes.

Title: Tricellulin constitutes a novel barrier at tricellular contacts of epithelial cells.

Source: J Cell Biol

Abstract: For epithelia to function as barriers, the intercellular space must be sealed. Sealing two adjacent cells at bicellular tight junctions (bTJs) is well described with the discovery of the claudins. Yet, there are still barrier weak points at tricellular contacts, where three cells join together. In this study, we identify tricellulin, the first integral membrane protein that is concentrated at the vertically oriented TJ strands of tricellular contacts. When tricellulin expression was suppressed with RNA interference, the epithelial barrier was compromised, and tricellular contacts and bTJs were disorganized. These findings indicate the critical function of tricellulin for formation of the epithelial barrier.

Discovery Description: Biomimetic materials based on Tricellulin may offer an alternative water purification membrane.

Title: Tight junction biology and kidney dysfunction.

Source: Am J Physiol Renal Physiol

**Abstract:** The epithelial tight junction (TJ) has three major functions. As a "gate," it serves as a regulatory barrier separating and maintaining biological fluid compartments of different composition. As a "fence," it generates and maintains the apicobasal polarity of cells that form the confluent epithelium. Finally, the TJ proteins form a trafficking and signaling platform that regulates cell growth, proliferation, differentiation, and dedifferentiation. Six examples are selected that illustrate the emerging link between TJ dysfunction and kidney disease. First, the glomerular slit diaphragm (GSD) is evolved, in part, from the TJ and, on maturation, exhibits all three functions of the TJ. GSD dysfunction leads to proteinuria and, in some instances, podocyte dedifferentiation and proliferation. Second, accumulating evidence supports epithelial-mesenchymal transformation (EMT) as a major player in renal fibrosis, the final common pathway that leads to end-stage renal failure. EMT is characterized by a loss of cell-cell contact and apicobasal polarity, which are hallmarks of TJ dysfunction. Third, in autosomal dominant polycystic kidney disease, mutations of the polycystins may disrupt their known interactions with the apical junction complex, of which the TJ is a major component. This can lead to disturbances in epithelial polarity regulation with consequent abnormal tubulogenesis and cyst formation. Fourth, evidence for epithelial barrier and polarity dysregulation in the pathogenesis of ischemic acute renal failure will be summarized. Fifth, the association between mutations of paracellin-1, the first TJ channel identified, and clinical disorders of magnesium and calcium wasting and bovine renal fibrosis will be used to highlight an integral TJ protein that can serve multiple TJ functions. Finally, the role of WNK4 protein kinase in shunting chloride across the TJ of the distal nephron will be addressed.

**Discovery Description:** Epithelial tight junctions may offer a mechanism for adaptive water purification membranes.

**Title:** Biomolecule separation by steric hindrance using nanofluidic filters.

**Source:** Conf Proc IEEE Eng Med Biol Soc

**Abstract:** Micro/nanofluidics technologies can be used to solve toughest challenges in the biomolecule analysis. It is now possible to fabricate nanofluidic channels with the dimension of 30-500 nm, and these nanofluidic structures have been formerly used to separate large DNA

molecules where molecular dimension is larger than the nanofluidic filter gap size. In this work, we demonstrate separation of biomolecules (DNA and proteins) that are smaller than the nanofluidic filter gap size. This is possible due to the steric hindrance effect of the biomolecules; the entropy of biomolecules has to be decreased for the molecules to enter the nanofluidic filter, which leads to the free energy barrier for the molecular transport. Double stranded DNA molecules as small as 100 bp (approximately 34 nm extended length), as well as SDS-coated proteins have been separated in a nanofluidic channel that has the filter gap thickness between 60-120 nm. This result clearly shows the potential of using nanofluidic filters as a sieving medium for smaller biomolecules such as proteins. Compared with traditional random nanoporous materials such as gel or polymer monolith, nanofluidic channels can be made precisely to have a pre-determined 'pore' size and shape, which allows characterization and optimization of biomolecule separation process.

Discovery Description: Nanofluidic channels may be used as alternative strategies for the design of water purification membranes.

Title: Sealing the live part of the skin: the integrated meshwork of desmosomes, tight junctions and curvilinear ridge structures in the cells of the uppermost granular layer of the human epidermis.

Source: Eur J Cell Biol

Abstract: In the literature the question of whether a system structurally and functionally related to the barrier function of the tight junctions (TJs) of polarized epithelia exists in the epidermis has been and still is controversially discussed. We have systematically addressed this question in a study of the granular layer of fetal and adult human epidermis, combining different light and electron microscopic methods. We show that the lateral membranes of the cells of the stratum granulosum are connected by an extended subapical complex system integrating desmosomes and TJ structures identified as sites of close membrane-membrane contact and as regions of membrane-to-membrane apposition that in immunoelectron microscopy are positive for TJ marker proteins, notably occludin, indicative of an extended, probably continuous TJ barrier. In addition, we have noted in freeze-fractures of the apical membrane attaching this layer to the basalmost membrane of the stratum corneum an extended system integrating

desmosomes with intramembraneous ridge configurations that appear as strands, circles, lariats or complex meshworks showing numerous continuities with the desmosomes. In some regions this system interconnecting desmosomes with curvilinear ridge structures occupies the major part of the plasma membrane. The molecular organizations and possible functional contributions of both structural systems positioned at the border between the living portion of the epidermis and the corneal layer are discussed, in particular in relation to the formation of a stable association between the two layers and of a barrier to the paracellular flow of molecules and particles. It is also discussed whether similar structures occur in other keratinizing stratified squamous epithelia, in squamous metaplasias and in tumors derived from such tissues.

Discovery Description: Tight junctions as found in the epithelial cells may offer alternative strategies for the design of water purification barriers.

Title: Permeabilities of teleost and elasmobranch gill apical membranes: evidence that lipid bilayers alone do not account for barrier function.

Source: Am J Physiol Cell Physiol

Abstract: Teleosts and elasmobranchs faced with considerable osmotic challenges living in sea water, use compensatory mechanisms to survive the loss of water (teleosts) and urea (elasmobranchs) across epithelial surfaces. We hypothesized that the gill, with a high surface area for gas exchange must have an apical membrane of exceptionally low permeability to prevent equilibration between seawater and plasma. We isolated apical membrane vesicles from the gills of *Pleuronectes americanus* (winter flounder) and *Squalus acanthias* (dogfish shark) and demonstrated approximately sixfold enrichment of the apical marker, ADPase compared to homogenate. We also isolated basolateral membranes from shark gill (enriched 2.3-fold for Na-K-ATPase) and using stopped-flow fluorometry measured membrane permeabilities to water, urea, and NH<sub>3</sub>. Apical membrane water permeabilities were similar between species and quite low ( $7.4 \pm 0.7 \times 10^{-4}$  and  $6.6 \pm 0.8 \times 10^{-4}$  cm/s for shark and flounder, respectively), whereas shark basolateral membranes showed twofold higher water permeability ( $14 \pm 2 \times 10^{-4}$  cm/s). Permeabilities to urea and NH<sub>3</sub> were also low in apical membranes. Because of the much lower apical to basolateral surface area we conclude that the apical membrane represents an

effective barrier. However, the values we obtained were not low enough to account for low water loss (teleosts) and urea loss (elasmobranchs) measured in vivo by others. We conclude that there are other mechanisms which permit gill epithelia to serve as effective barriers. This conclusion has implications for the function of other barrier epithelia, such as the gastric mucosa, mammalian bladder, and renal thick ascending limb.

Discovery Description: Study of gill-type membranes in order to elucidate filter functions that are alternative to the apical structure might lead to the design of improved filters for water purification.

Title: An update of the defensive barrier function of skin.

Source: Yonsei Med J

Abstract: Skin, as the outermost organ in the human body, continuously confronts the external environment and serves as a primary defense system. The protective functions of skin include UV-protection, anti-oxidant and antimicrobial functions. In addition to these protections, skin also acts as a sensory organ and the primary regulator of body temperature. Within these important functions, the epidermal permeability barrier, which controls the transcutaneous movement of water and other electrolytes, is probably the most important. This permeability barrier resides in the stratum corneum, a resilient layer composed of corneocytes and stratum corneum intercellular lipids. Since the first realization of the structural and biochemical diversities involved in the stratum corneum, a tremendous amount of work has been performed to elucidate its roles and functions in the skin, and in humans in general. The perturbation of the epidermal permeability barrier, previously speculated to be just a symptom involved in skin diseases, is currently considered to be a primary pathophysiologic factor for many skin diseases. In addition, much of the evidence provides support for the idea that various protective functions in the skin are closely related or even co-regulated. In this review, the recent achievements of skin researchers focusing on the functions of the epidermal permeability barrier and their importance in skin disease, such as atopic dermatitis and psoriasis, are introduced.

Discovery Description: Biomimetic water filtration membranes might be based on the stratum corneum.



Title: Molecular packing in network-forming collagens.

Source: Adv Protein Chem

Abstract: Different collagen types can vary considerably in length, molecular weight, chemical composition, and the way they interact with each other to form molecular aggregates. Collagen Types IV, VI, VIII, X, and dogfish egg case collagen make linear and lateral associations to form open networks rather than fibers. The roles played by these network-forming collagens are diverse: they can act as support and anchorage for cells and tissues, serve as molecular filters, and even provide protective permeable barriers for developing embryos. Their functional properties are intimately linked to their molecular organization. This Chapter reviews what is known about the molecular structure of this group of collagens, describes the ways the molecules interact to form networks, and-despite the large variations in molecular size-identifies common aggregation themes.

Discovery Description: New water purification filter materials could be based on collagen-like materials.

Title: On the filter-feeding of *Doliolum* (Tunicata: Thaliacea)

Source: JOURNAL OF EXPERIMENTAL MARINE BIOLOGY AND ECOLOGY

Abstract: Filter feeding in doliolids is re-described. Feeding involves the dorsal spiral volute of the peripharyngeal bands, which rotates the filter in the pharynx so that particles inhaled are trapped between two layers of the mucous filter. The process is more complex than in salps and is akin to that found in young stages of the aplousobranch ascidian *Clavelina*. Feeding proceeds normally after removal of the brain and is controlled by a small visceral nervous system (linked to the brain by a small posterior visceral nerve). This visceral nervous system controls the activity of the cilia of the gills, peripharyngeal bands and oesophagus, and the production of the feeding filter by the endostyle. Analysis of video records has shown that in the two life cycle stages examined, maximum particle entry velocity to the filter was  $600 \mu\text{m s}^{-1}$ . Lateral area of the filter was estimated at  $1.15 \text{ mm}^2$  hence mean flow velocity across the filter was up to  $170 \mu\text{m s}^{-1}$ .

Direct measurements of the filter mesh have not been obtained: calculations are discussed of volumes filtered daily, and of mesh size (based on the pressure drops across the filters of ascidian tunicates). It is concluded that there are wide variations in the filtration rates of doliolids. (C) 1997 Elsevier Science B.V..

Discovery Description: Self cleaning water purification filters might be designed based on filter feeding principles.

Title: Comparative ecophysiology of active zoobenthic filter feeding, essence of current knowledge

Source: JOURNAL OF SEA RESEARCH

Abstract: The present contribution gives an overview of current knowledge of a comprehensive and steadily growing research field. The first section deals with water pumping and particle retention mechanisms in ciliary and muscular filter feeders. The second section examines the biological filter pumps in order to assess adaptation to the environment. Filter-feeding benthic invertebrates have evolved filter pumps to solve common basic problems. This has led to a large degree of similarity between otherwise distant standing species, which makes comparative studies interesting and important. The present review of zoobenthic filter feeding aims at accentuating such recognition. (C) 2000 Elsevier Science B.V. All rights reserved.

Discovery Description: Self cleaning water purification filters might be designed based on filter feeding principles.

Title: Feeding in a calcareous sponge: Particle uptake by pseudopodia

Source: BIOLOGICAL BULLETIN

Abstract: Sponges are considered to be filter feeders like their nearest protistan relatives, the choanoflagellates. Specialized "sieve" cells (choanocytes) have an apical collar of tightly spaced, rodlike microvilli that surround a long flagellum. The beat of the flagellum is believed to draw

water through this collar, but how particles caught on the collar are brought to the cell surface is unknown. We have studied the interactions that occur between choanocytes and introduced particles in the large feeding chambers of a syconoid calcareous sponge. Of all particles, only 0.1- $\mu\text{m}$  latex microspheres adhered to the collar microvilli in large numbers, but these were even more numerous on the choanocyte surface. Few large particles (0.5- and 1.0- $\mu\text{m}$  beads and bacteria) contacted the collar microvilli; most were phagocytosed by lamellipodia at the lateral or apical cell surface, and clumps of particles were engulfed by pseudopodial extensions several micrometers from the cell surface. Although extensions of the choanocyte apical surface up to 16  $\mu\text{m}$  long were found, most were 4  $\mu\text{m}$  long, twice the height of the collar microvilli. These observations offer a different view of particle uptake in sponges, and suggest that, at least in syconoid sponges, uptake of particles is less dependent on the strictly sieving function of the collar microvilli.

Discovery Description: New water filtration systems could be crafted based on the user of choanocytes.

Title: Ciliary feeding structures and particle capture, mechanism in the freshwater bryozoan

Source: INVERTEBRATE BIOLOGY

Abstract: In contrast to marine bryozoans, the lophophore structure and the ciliary filter-feeding mechanism in freshwater bryozoans have so far been only poorly described. Specimens of the phylactolaemate bryozoan *Plumatella repens* were studied to clarify the tentacular ciliary structures and the particle capture mechanism. Scanning electron microscopy revealed that the tentacles of the lophophore have a frontal band of densely packed cilia, and on each side a zigzag row of laterofrontal cilia and a band of lateral cilia. Phalloidin-linked fluorescent dye showed no sign of muscular tissue within the tentacles. Video microscopy was used to describe basic characteristics of particle capture. Suspended particles in the incoming water flow, set up by the lateral 'pump' cilia on the tentacles, approach the tentacles with a velocity of 1-2  $\text{mm s}^{-1}$ . Near the tentacles, the particles are stopped by the stiff sensory laterofrontal cilia acting as a mechanical sieve, as previously seen in marine bryozoans. The particle capture mechanism suggested is based on the assumed ability of the sensory stiff laterofrontal

cilia to be triggered by the deflection caused by the drag force of the through-flowing water on a captured food particle. Thus, when a particle is stopped by the laterofrontal cilia, the otherwise stiff cilia are presumably triggered to make an inward flick which brings the restrained particle back into the downward directed main current, possibly to be captured again further down in the lophophore before being carried to the mouth via the food groove. No tentacle flicks and no transport of captured particles on the frontal side of the tentacles were observed. The velocity of the metachronal wave of the water-pumping lateral cilia was measured to be similar to  $0.2 \text{ mm s}^{-1}$ , the wavelength was similar to  $7 \text{ }\mu\text{m}$ , and hence the ciliary beat frequency estimated to be similar to  $30 \text{ Hz}$  (similar to  $20 \text{ }^{\circ}\text{C}$ ). The filter feeding process in *P. repens* reported here resembles the ciliary sieving process described for marine bryozoans in recent years, although no tentacle flicks were observed in *P. repens*. The phylogenetic position of the phylactolaemates is discussed in the light of these findings.

Discovery Description: Biomimetic cilia structures could be used as a mean to prevent membrane fouling.

Title: Molecular basis of proteinuria.

Source: Adv Anat Pathol

Abstract: The glomerular filtration barrier is composed of endothelial cells, basement membrane, and podocytes. In recent years, remarkable progress has been made in our understanding of the molecular structure of the filtration barrier and its relation to the effectiveness of the barrier function. The glomerular basement membrane is composed of a multitude of proteins, including collagen IV, heparan sulfate proteoglycans, and laminin, among others. The slit diaphragm, which is seen as a membrane covering the space between adjacent foot processes close to the basement membrane, is an extremely important structure with a crucial role in permselectivity of the filtration barrier. Its composition is now understood to consist primarily of a unique protein called nephrin. Mutations in the gene-encoding nephrin are known to result in the Finnish type of nephrotic syndrome. The exact mechanism by which nephrin controls permselectivity is not yet clear, but it is known to interact with several podocyte proteins including CD2AP, podocin, and alpha-actinin-4. Abnormalities of any of these proteins may result in proteinuria. The role of nephrin and its associated proteins in the

pathogenesis of common acquired glomerulopathies in humans is still under investigation. Normal function of podocyte also depends upon maintaining a fully mature and terminally differentiated phenotype. A host of transcription factors, especially WT1 and PAX2, play a significant role in modulating podocyte function.

Discovery Description: A new water purification methodology might be based on the glomerular filtration barrier.

## APPENDIX 13 – CATARACTS CORE LITERATURE

This appendix summarizes the Cataracts core literature restricted to select semantic classes. While this is not discovery, since Cataracts is mentioned in each record, nevertheless, there is substantial value in collecting this information in one place. Due to time restrictions, we present article citations only.

The query used to retrieve the Cataracts core literature was restricted to **non-drug** semantic classes, similar conceptually to what was used in Chapter 5. The main difference is that the query used for this appendix contained more non-drug semantic classes than was the case for Chapter 5, but a few less classes than was the case for Appendix 6.. The query used for this appendix may be written as:

(PLANTS, MEDICINAL [MH] OR PLANTS, EDIBLE [MH] OR "PLANT EXTRACTS" [MH] OR "PLANT PREPARATIONS" [MH] OR "PLANT OILS" [MH] OR PHYTOTHERAPY [MH] OR FRUIT [MH] OR VEGETABLES [MH] OR "FISH OILS" [MH] OR ALGAE [MH] OR NUTS [MH] OR "DAIRY PRODUCTS" [MH] OR FATS [MH] OR DIET [MH] OR FLAVONOIDS [MH] OR "DIETARY SUPPLEMENTS" [MH] OR Plants [MH] OR Plankton [MH] OR Plant Components [MH] OR Plant Families and Groups [MH] OR Seedling [MH] OR Trees [MH] OR Algae [MH] OR Algae, Brown [MH] OR Algae, Golden-Brown [MH] OR Algae, Green [MH] OR Algae, Red [MH] OR Lichens [MH] OR Seaweed [MH]) AND (Cataract\*)

where the non-drug phrases in CAPS are those used in the Chapter 5 core query, and the lower case phrases are those added for this appendix. There are undoubtedly more non-drug semantic classes that could be added, but we believe the present query provides a good representation of the total core Cataracts non-drug literature.

We entered the query into the PubMed search engine, and retrieved 385 records with Abstracts. The citation for each of the 385 records is as follows:

1: Huang HY, Caballero B, Chang S, Alberg A, Semba R, Schneyer C, Wilson RF,

- Cheng TY, Prokopowicz G, Barnes GJ 2nd, Vassy J, Bass EB.  
Multivitamin/mineral supplements and prevention of chronic disease.  
Evid Rep Technol Assess (Full Rep). 2006 May;(139):1-117. Review.  
PMID: 17764205 [PubMed - indexed for MEDLINE]
- 2: Bialek-Szymanska A, Misiuk-Hojlo M, Witkowska K.  
[Risk factors evaluation in age- related macular degeneration]  
Klin Oczna. 2007;109(4-6):127-30. Polish.  
PMID: 17725268 [PubMed - indexed for MEDLINE]
- 3: Nagai N, Ito Y, Tai H, Hataguchi Y, Nakagawa K.  
Effects of magnesium content in the feed on cataract development in  
Shuniya  
cataract rat.  
J Oleo Sci. 2006;56(1):29-33.  
PMID: 17693696 [PubMed - indexed for MEDLINE]
- 4: Delcourt C.  
Application of nutrigenomics in eye health.  
Forum Nutr. 2007;60:168-75. Review.  
PMID: 17684413 [PubMed - indexed for MEDLINE]
- 5: Suryanarayana P, Saraswat M, Petrash JM, Reddy GB.  
Emblica officinalis and its enriched tannoids delay streptozotocin-induced  
diabetic cataract in rats.  
Mol Vis. 2007 Jul 24;13:1291-7.  
PMID: 17679931 [PubMed - indexed for MEDLINE]
- 6: Biju PG, Rooban BN, Lija Y, Devi VG, Sahasranamam V, Abraham A.  
Drevogenin D prevents selenite-induced oxidative stress and calpain  
activation in  
cultured rat lens.  
Mol Vis. 2007 Jul 12;13:1121-9.  
PMID: 17653057 [PubMed - indexed for MEDLINE]
- 7: Cao XG, Li XX, Bao YZ, Xing NZ, Chen Y.  
Responses of human lens epithelial cells to quercetin and DMSO.  
Invest Ophthalmol Vis Sci. 2007 Aug;48(8):3714-8.  
PMID: 17652743 [PubMed - indexed for MEDLINE]

8: Rodeheffer C, von Messling V, Milot S, Lepine F, Manges AR, Ward BJ.  
Disease manifestations of canine distemper virus infection in ferrets are modulated by vitamin A status.

J Nutr. 2007 Aug;137(8):1916-22.

PMID: 17634264 [PubMed - indexed for MEDLINE]

9: Rodriguez-Rodriguez E, Ortega RM, Lopez-Sobaler AM, Aparicio A, Bermejo LM, Marin-Arias LI.

The relationship between antioxidant nutrient intake and cataracts in older people.

Int J Vitam Nutr Res. 2006 Nov;76(6):359-66.

PMID: 17607955 [PubMed - indexed for MEDLINE]

10: Raju TN, Kanth VR, Reddy PU.

Influence of kynurenines in pathogenesis of cataract formation in tryptophan-deficient regimen in Wistar rats.

Indian J Exp Biol. 2007 Jun;45(6):543-8.

PMID: 17585690 [PubMed - indexed for MEDLINE]

11: Lu M, Taylor A, Chylack LT Jr, Rogers G, Hankinson SE, Willett WC, Jacques PF.

Dietary linolenic acid intake is positively associated with five-year change in eye lens nuclear density.

J Am Coll Nutr. 2007 Apr;26(2):133-40.

PMID: 17536124 [PubMed - indexed for MEDLINE]

12: Ghosh D, Konishi T.

Anthocyanins and anthocyanin-rich extracts: role in diabetes and eye function.

Asia Pac J Clin Nutr. 2007;16(2):200-8. Review.

PMID: 17468073 [PubMed - indexed for MEDLINE]

13: Townend BS, Townend ME, Flood V, Burlutsky G, Rochtchina E, Wang JJ, Mitchell P.

Dietary macronutrient intake and five-year incident cataract: the blue mountains



eye study.

Am J Ophthalmol. 2007 Jun;143(6):932-939. Epub 2007 Apr 24.

PMID: 17459316 [PubMed - indexed for MEDLINE]

14: Aucamp PJ.

Questions and answers about the effects of the depletion of the ozone layer on

humans and the environment.

Photochem Photobiol Sci. 2007 Mar;6(3):319-30. Epub 2007 Feb 1.

PMID: 17344966 [PubMed - indexed for MEDLINE]

15: Li W, Wei CV, White PJ, Beta T.

High-amylose corn exhibits better antioxidant activity than typical and waxy

genotypes.

J Agric Food Chem. 2007 Jan 24;55(2):291-8.

PMID: 17227056 [PubMed - indexed for MEDLINE]

16: Farag AM, Nimick DA, Kimball BA, Church SE, Harper DD, Brumbaugh WG.

Concentrations of metals in water, sediment, biofilm, benthic macroinvertebrates,

and fish in the Boulder River watershed, Montana, and the role of colloids in metal uptake.

Arch Environ Contam Toxicol. 2007 Apr;52(3):397-409. Epub 2007 Jan 11.

PMID: 17219028 [PubMed - indexed for MEDLINE]

17: Seddon JM.

Multivitamin-multimineral supplements and eye disease: age-related macular

degeneration and cataract.

Am J Clin Nutr. 2007 Jan;85(1):304S-307S. Review.

PMID: 17209215 [PubMed - indexed for MEDLINE]

18: Huang R, Shi F, Lei T, Song Y, Hughes CL, Liu G.

Effect of the isoflavone genistein against galactose-induced cataracts in rats.

Exp Biol Med (Maywood). 2007 Jan;232(1):118-25.

PMID: 17202592 [PubMed - indexed for MEDLINE]

19: Kador PF, Betts D, Wyman M, Blessing K, Randazzo J.

Effects of topical administration of an aldose reductase inhibitor on cataract formation in dogs fed a diet high in galactose.

Am J Vet Res. 2006 Oct;67(10):1783-7.

PMID: 17014334 [PubMed - indexed for MEDLINE]

20: Williams DL.

Oxidation, antioxidants and cataract formation: a literature review.

Vet Ophthalmol. 2006 Sep-Oct;9(5):292-8.

PMID: 16939456 [PubMed - indexed for MEDLINE]

21: Kato A, Higuchi Y, Goto H, Kizu H, Okamoto T, Asano N, Hollinshead J, Nash

RJ, Adachi I.

Inhibitory effects of Zingiber officinale Roscoe derived components on aldose

reductase activity in vitro and in vivo.

J Agric Food Chem. 2006 Sep 6;54(18):6640-4.

PMID: 16939321 [PubMed - indexed for MEDLINE]

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Lutein and zeaxanthin and the risk of cataract: the Melbourne visual impairment project.

Invest Ophthalmol Vis Sci. 2006 Sep;47(9):3783-6.

PMID: 16936087 [PubMed - indexed for MEDLINE]

23: Dawczynski J, Winnefeld K, Konigsdorffer E, Augsten R, Blum M, Strobel J.

[Selenium and cataract--risk factor or useful dietary supplement?]

Klin Monatsbl Augenheilkd. 2006 Aug;223(8):675-80. German.

PMID: 16927224 [PubMed - indexed for MEDLINE]

24: Huang HY, Caballero B, Chang S, Alberg AJ, Semba RD, Schneyer CR, Wilson RF,

Cheng TY, Vassy J, Prokopowicz G, Barnes GJ 2nd, Bass EB.

The efficacy and safety of multivitamin and mineral supplement use to prevent

cancer and chronic disease in adults: a systematic review for a National Institutes of Health state-of-the-science conference.

Ann Intern Med. 2006 Sep 5;145(5):372-85. Epub 2006 Jul 31. Review.

PMID: 16880453 [PubMed - indexed for MEDLINE]

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Nutritional antioxidants and age-related cataract and maculopathy.

Exp Eye Res. 2007 Feb;84(2):229-45. Epub 2006 Jul 31. Review.

PMID: 16879819 [PubMed - indexed for MEDLINE]

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Classical galactosaemia revisited.

J Inherit Metab Dis. 2006 Aug;29(4):516-25. Epub 2006 Jul 11. Review.

PMID: 16838075 [PubMed - indexed for MEDLINE]

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Influence of tobacco use on cataract development.

Br J Ophthalmol. 2006 Nov;90(11):1374-7. Epub 2006 Jul 12.

PMID: 16837540 [PubMed - indexed for MEDLINE]

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Ingestion of IH636 grape seed proanthocyanidin extract to prevent selenite-induced oxidative stress in experimental cataract.

J Cataract Refract Surg. 2006 Jun;32(6):1041-5.

PMID: 16814068 [PubMed - indexed for MEDLINE]

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The effect of the presence of globular proteins and elongated polymers on enzyme activity.

Biochim Biophys Acta. 2006 Jun;1764(6):1000-6. Epub 2006 Jan 26.

PMID: 16720113 [PubMed - indexed for MEDLINE]

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JP.

The Antioxidants in Prevention of Cataracts Study: effects of antioxidant supplements on cataract progression in South India.

Br J Ophthalmol. 2006 Jul;90(7):847-51. Epub 2006 Mar 23.

PMID: 16556618 [PubMed - indexed for MEDLINE]

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PMID: 16440613 [PubMed - indexed for MEDLINE]
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PMID: 16396685 [PubMed - indexed for MEDLINE]
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J Chromatogr A. 2006 Apr 21;1112(1-2):3-22. Epub 2006 Jan 18. Review.  
PMID: 16388813 [PubMed - indexed for MEDLINE]
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Evidence for the use of nutritional supplements and herbal medicines in common eye diseases.  
Am J Ophthalmol. 2006 Jan;141(1):157-66. Review.  
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